NEURAL AND BEHAVIORAL SENSITIVITY TO BOUNDARY CUES ACROSS TYPICAL AND ATYPICAL DEVELOPMENT

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ABSTRACT

Boundaries are fundamental features that define a scene and contribute to its geometric shape. For example, four-year-olds reorient in accord with the geometry of a layout defined by a curb that is 2 cm high, but fail to do so when the curb is replaced by a flat mat on the floor (Lee & Spelke, 2011). Our previous research using fMRI showed a similar distinct sensitivity to boundaries in scene representation by the healthy adult brain (Ferrara & Park, 2014). In the present research, I aim to determine whether this finely tuned sensitivity to boundaries may be impaired by genetic deficit. Behavioral (Experiment 1) and neuroimaging (Experiment 2) methods are used to study individuals with Williams syndrome (WS), a developmental disorder characterized by a profile of severe impairment in a range of spatial functions.

In Experiment 1, individuals with WS and typically developing (TD) age-matched controls were disoriented and then recovered a hidden target in three different types of arrays that varied in terms of boundary cue: a Mat, a Curb and full Walls. Unlike TD controls, who reoriented geometrically in all three arrays, people with WS only reliably used geometry in the Wall condition. In Experiment 2, we measured fMRI activity in scene-selective regions of the same WS and TD participants. Scene stimuli were used that mirrored the physical boundary arrays of Experiment 1: a Mat, a Curb, and a Wall. In TD controls, the parahippocampal place area (PPA) showed increases in activity from the Mat, to Curb, to Wall. In WS participants however, PPA activity did not distinguish between the Mat and Curb. Multivoxel pattern analyses using a linear classifier confirmed this difference between the two participant groups. Taken together, these results reveal one of the crucial aspects of scene representation that is manifested

behaviorally as fine-grained sensitivity to slight boundary cues in reorientation. Using WS as a test case, we find that atypical patterns of reorientation correspond with less fine-grained distinction at the neural level. By coupling behavioral and neuroimaging methods, this research sheds light on the connection between scene representation in the brain and fluid navigation in behavior.

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CHAPTER 1: INTRODUCTION

The cognitive processes that enable us to navigate from place to place operate so fluidly and without effort that one might assume a single unitary underlying mechanism. In fact however, research with animals and humans indicates that proficient navigation is a complex process that seamlessly integrates input from a number of sources and types of spatial cues (e.g., landmarks, features, and geometric structure). Neuroimaging evidence points to separable neural systems for navigation by the boundaries of an environment vs. navigation by landmarks within an environment (Doeller & Burgess, 2008). As we make our way from one place to the next, what feels to be a seamless and effortless process at the behavioral level is in fact the product of multiple computations achieved by integrating various inputs from numerous sensory systems and cortical areas (e.g., information about orientation, movement and balance from the vestibular system and proprioception, visual information about scene layout and landmarks from the parahippocampal place area and retrosplenial complex (Epstein, Graham, & Downing, 2003; Park & Chun, 2009), as well as allocentric spatial information, which provides a reference frame independent of the viewer's position (Klatsky, 1998)). These inputs contribute to the creation of a cognitive map of the environment, which codes its landmarks, paths, and their spatial relationships (Bennett, 1996; Gallistel, 1990; Maguire et al., 1998; O'Keefe & Nadel, 1978; Tolman, 1948).[1] Because these multiple types of navigationally relevant information are so cohesively integrated in the healthy adult brain, it is difficult to tease them apart to understand the meaningful components of the functional architecture and supporting neural systems.

[1] However, the ability to learn and navigate large-scale environments shows marked individual differences (Wolbers & Hegarty, 2010), and there is still debate in the literature as to whether humans use cognitive maps or rely on snapshot memories of locations and route-following response strategies for navigation (Wang & Spelke, 2002; Foo et al., 2005; Shettleworth, 2010).

A great deal of research using a variety of methods points to environmental boundaries as an important cue for navigation by humans of all ages and many nonhuman species. In the present research, I focus on boundaries as a fundamental spatial cue in both navigation and the visual processing of scenes. I ask whether the spatial navigation deficit associated with Williams syndrome (WS, a genetic disorder) leads to impaired use of boundaries in reorientation, and whether these behavioral impairments are in turn linked to qualitatively different patterns of scene representation in the brain. By coupling behavioral and neuroimaging methods, this research sheds light on not only the WS spatial deficit, but also provides insight to a potential connection between the bases of scene representation at the neural level and fluid navigation at the behavioral level. Specifically, I hypothesize that unique encoding of different types of environmental boundaries in scene-selective cortices supports their flexible use in reorientation. If scene-selective areas are unable to encode crucial differences in different types of boundaries (i.e., varying degrees of vertical structure), the ability to use these cues in navigation may suffer as a result. Given documented abnormalities in reorientation, the WS population offers a unique test case for this hypothesis.

Overview of the dissertation

In Chapter 2, I first review research employing a variety of methods that points to the universally important role of environmental boundaries in navigation by animals, human children, and adults. A broad overview of the neural bases of navigation is then provided, with specific attention to findings that suggest specialized neural mechanisms for the encoding and representation of boundaries. I next summarize the relevant findings to identify five contributing factors to what constitutes an effective boundary. The final section of

Chapter 2 describes the case of people with WS, as well as the structural and functional neural abnormalities relevant to their impairments in spatial navigation. Chapter 3 details the method and results of Experiment 1, which tests reorientation by three different types of boundaries in TD children, adults, and individuals with WS. Using visual stimuli that approximate the boundary arrays used in Experiment 1, Experiment 2 (Chapter 4) explores the neural representation of these boundaries at the neural level in individuals with WS and TD adults. Chapter 5 concludes with a general discussion of these findings and their implications.

CHAPTER 2: BACKGROUND

Use of boundaries in navigation

The ability to make our way from one location to the next, for example from the security line at the airport to our particular departure gate, is essential for successful function in our everyday lives. Accurate navigation was likely even more crucial for our evolutionary ancestors, whose survival depends on navigation between places that provide sustenance and shelter. The ability to make our way effortlessly through space is a capacity that most of us take for granted. In fact however, proficient navigation is a complex process that seamlessly integrates input from a number of sources.

There are several different mechanisms and underlying computations through which successful navigation may be achieved. In *path integration*, an organism specifies a target's location in terms of its relationship to itself. If the organism moves, it is able to update its relative position to the target through calculation of the alterations in distance and angle that have occurred as a result of its changed location (also known as *dead-reckoning*). This updated position may be accomplished by using internal cues from the organism's movement or external cues from the environment (e.g., Gallistel, 1990; Newcombe & Huttenlocher, 2000; Reiser, Pick, Ashmead, & Garing, 1995). In *beacon homing*, an organism represents a position in space by making use of an object that is directly visible (or detectable through other modalities, such as smell). There is a distinction to be made between navigation towards a beacon, which specifically marks a target's location, and navigation in relation to a *landmark*, which is a salient aspect of the environment (distinguishable object, or property such as color or odor) which acts as a referent to indicate location at a certain distance and/or direction from the target (e.g., Gallistel, 1990; Newcombe, 2006; Sutton, 2006).

In the present research, I focus on boundaries as elements of the external environment that are important cues for navigation. A boundary may be generally defined as an extended surface that separates the local environment from other environments (e.g., walls of a room) (Mou & Zhou, 2013). A boundary can also be a division in the navigable surface that prevents you from moving forward, for example, the functional line between the concrete pavement and the water of the pool is a very salient boundary for a child who has not yet learned how to swim. The features that qualify a true boundary as such is a topic to which I will later return, but at present this example serves to show that, as mobile organisms, the boundaries in our environment are something that we must constantly be aware of in order to avoid undesirable consequences (trying to walk through a sliding glass door, etc.) Indeed, boundaries are so fundamental that the brain has regions dedicated to their processing, even at the level of specialized neurons (i.e., boundary vector cells).

In fact, boundaries are one of the salient cues that we rely on to achieve each of the different types of navigation described above. For example, in path integration, one may update one's position by means of calculating the distance traveled along a nearby wall. In beacon homing, we might calculate our distance to Gilman hall by means of focusing on the strong vertical boundary of its façade. And finally, boundaries may also be used as landmarks, as one may recall that she parked her car to the right of the red brick wall. These examples provide general descriptions of how one may use boundaries to navigate and represent a unique spatial location. Navigation by boundaries is an ability that has also been extensively studied in the laboratory.

Using boundaries to represent spatial location

The Morris water maze (Morris, 1981) is a task that was designed to investigate how

animals learn to navigate to a particular spatial location. In this task, rats are required to learn the location of a hidden platform submerged beneath opaque liquid that fills a circular pool. Because the target of the platform is not visible, beacon homing is not possible. The rat must use other landmarks or external cues in the environment to represent the location of the hidden platform, and update its relative position accordingly. Many studies using the Morris water maze predominantly focus on rats' ability to use distal cues (i.e., the walls of the lab room, or cues that are otherwise removed from the behavioral apparatus) (e.g., McGauran et al., 2004; Prados & Trobalon, 1998; Rodrigo et al., 1997; Whishaw & Mittleman, 1986). However, other research has shown that rats also use proximal intra-maze cues, such as the boundaries of the apparatus, objects placed around the pool, or unique surface textures, to help them swim to the submerged platform (e.g., Akers et al., 2007; Hayward et al., 2003; Hamilton et al., 2008). (See Knierim & Hamilton (2011) for a full review of proximal vs. distal cues in the Morris water maze.) As Knierim and Hamilton (2011) note, the proximal-distal axis is a continuum, and some cases are inherently ambiguous by this definition. Taken as a whole, research using the Morris water maze serves to show that boundaries are so salient and so fundamental a cue to navigation that they operate effectively as either proximal (walls of the pool apparatus) or distal (walls of the laboratory room) cues.

But when it comes down to it, which is more immediately important for spatial navigation, a proximal boundary, or a distal one? To investigate this question, Hamilton et al. (2007) introduced a twist to the original Morris water maze paradigm: once rats had been trained to learn the location of the hidden platform, the experimenters translated the pool's position within the laboratory room so that the platform was now located on the directly opposite side of the pool from its original position. A probe trial in which no platform was

present was conducted at this point, to determine where rats would swim to expect to find the submerged platform. On this probe trial, rats swam directly to the location of the platform as defined by the local boundaries of the pool apparatus, instead of the distal boundaries of the laboratory room walls. Rats persisted in swimming at the relative pool-based location, clearly demonstrating their expectation that the submerged platform should be found at that place in the pool. This indicates a preference to navigate according to relative location as defined by the local boundaries of the apparatus, rather than absolute location as defined by the distal boundaries that set the reference frame of the room. Human performance in a virtual-reality version of the Morris water maze is consistent with this pattern. Even when the height of the pool wall was reduced to only a few centimeters above the water, human participants still demonstrated preferential use of the local apparatus boundary over the room reference frame when attempting to navigate to the location of the hidden platform. Interestingly, when Hamilton et al. (2009) further reduced the height of the local pool boundary so that it was rendered entirely invisible (flush with the surface of the water), the majority of participants demonstrated confusion and were only able to locate the hidden platform by taking circuitous and non-direct paths, all the way up to the final block of training. In their review of these findings, Knierim and Hamilton (2011) propose that distal cues have a predominant role of setting an animal's orientation, rather than defining specific spatial locations. For the latter, they argue that local boundaries and self-motion cues (path integration) play the dominant role.

The Morris water maze is just one spatial navigation task of many that highlights the way in which boundaries are used as cues in navigation. The subsequent section focuses on a

different aspect of navigation not yet discussed, in which boundaries play perhaps an even more prominent role.

Boundaries and geometric reorientation

The geometric module

When it is possible for an organism to visually track its own movements through space, beacon-homing, dead reckoning, and path integration may each be employed successfully. However, there is a specific situation that I have yet to address. What does an organism do when it has completely lost its sense of direction, and is no longer sure of what way it's facing? In these circumstances, previously integrated path information is no longer useful, and the organism's internal sense of heading is inaccessible or rendered inaccurate. The recovery of one's sense of position and direction is a crucial ability for all mobile organisms, especially in relation to an important goal location such as 'home' or 'food source.' This ability, termed *reorientation*, is the focus of the present thesis research.

How do animals accomplish reorientation? A seminal study by Cheng and Gallistel provided groundbreaking evidence to answer this question (Cheng & Gallistel 1984; Cheng 1986). In this paradigm, rats were shown the location of food that had been buried under the pine chips of their cage (Figure 2.1, at the corner labeled *C* for correct). They were allowed to eat some of it, were then removed from the cage so that the food could be re-buried, and finally were released back into the cage to dig out the food once more. Their digging at a particular location thus provided a clear indication of where they believed the food to be. To help the rats disambiguate one location from another, Cheng placed panels that differed in smell, texture, and appearance in each of the four corners. One panel was smooth and had a stripe down the center, one was covered in shiny aluminum, one was rough and made to

smell like peppermint, and another emitted a bright light and smelled like anise. It was expected that rats would pair the distinctive cue at the target corner with the location of the hidden food, and subsequently use this information to inform where they should dig. Although rats did learn to dig at the location of the food (.55 of their total searches were made to corner *C*, see Figure 2.1), they also made a surprising number of errors at the corner that was the 180° rotational equivalent of the correct location (.35 of searches made to the corner labeled *R* for rotational equivalent).

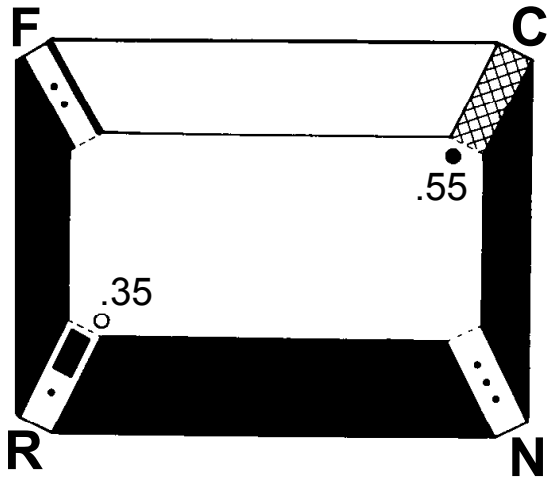

Figure 2.1: Percentage of trials on which an individual rat dug at the correct location (*C*) or made a rotational error (*R*). The remaining 10% of searches were made to the corner located near to the correct one (*N*), or far from the correct one (*F*). Figure modified from Cheng (1986).

What could account for the rats' seemingly odd performance? Cheng and Gallistel realized that instead of directly pairing the target corner of the food with its distinctive color or smell, the rats were orienting themselves in accord with the metric relations of the space (length of the walls), in combination with sense relations (left and right). The combination of left/right sense, along with judgments of the relative lengths of the walls, will fail to provide information that is sufficient to distinguish the correct corner from its diagonal opposite. Clearly, the rats were not using the unique smell, texture, or color of each corner to help them

identify the location of the food. Otherwise, they would have been able to dig at the correct corner far more often than they did. Why are aspects such as smell, color, and texture ignored, while information about left/right sense and wall length is faithfully followed? These forms of information are in fact quite different from one another. Smell, color, and texture are all surface features. In isolation they don't tell us anything about the location of an object in space (e.g., simply knowing that my notebook is blue doesn't tell me where it may be located on my desk). In contrast, the lengths of the walls of an indoor enclosure and their relationship to one another conveys information about the geometry of an environment. Although this does encode some information about spatial location, is not sufficient to uniquely identify specific locations in symmetric environments (illustrated by the rotational corner confusion made by Cheng's rats).

Because the rats so often chose to dig at the rotationally equivalent corner, we see that geometry outweighed features as the information of choice when they had to reestablish their heading. Based upon this finding, Cheng and Gallistel (1986) proposed the existence of a mechanism that they termed the "geometric module." They concluded that the geometric module extracts the geometry of an environment by computing the major and minor axes of a space to form an encapsulated representation. This representation does not include the featural information of landmarks, and takes "no account of the smells emanating from surfaces, their reflective or luminance characteristics, their texture, and so on" (Gallistel, 1990, p. 208). The issue of whether the encoding of geometric information possesses the true characteristics of a module (sensu Fodor, 1983) is under debate (e.g., Cheng, 2008; Cheng & Newcombe, 2005; Learmonth, Newcombe, & Huttenlocher, 2001; Lee & Spelke, 2011). But since Cheng and Gallistel's original study, subsequent research has demonstrated the primacy

of geometry for reorientation by human adults, young children, monkeys, birds, and fish (Gouteux, Thinus-Blanc & Vauclair, 2001; Hermer & Spelke, 1994, 1996; Kelly, Spetch & Heath, 1998; Learmonth, Newcombe & Huttenlocher, 2001; Sovrano, Bisazza & Vallortigara, 2003; Tommasi et al., 2012; Vallortigara, Zanforlin & Pasti, 1990; Vargas, Lopez, Salas, & Thinus-Blanc, 2004). The use of non-geometric information, such as landmarks or wall luminance, varies across species and tasks, but room-shape geometry is used consistently.

Boundaries and geometry

Having discussed the behavioral phenomenon of geometric reorientation, I will now take a step back to consider what exactly are the 'geometric' properties of an environment. To gain traction on this question, I will first consider the nature of the mechanism by which geometry is used to achieve reorientation.

Gallistel originally proposed that "there is an organ (neural system) of the rat brain dedicated to the computational task of finding a congruence between the Euclidean shape of the space the animal now perceives and the remembered shape of the environment" (Gallistel, 1990, p. 208). Cheng's data do not support the interpretation that the rats establish local correspondences by pairing points in the currently perceived space and the remembered space on the basis of smell, feel, brightness, etc. Instead, Gallistel proposes that the rats used a "global parameter-matching algorithm" that depends on global, not local, representations of environmental shape. More recent research provides evidence that is very much in line with this account. Huttenlocher and colleagues have analyzed the search patterns of children during the realignment stage of reorientation that Gallistel describes. Children are not likely to survey the space of the room by turning their bodies or heads to view multiple walls and

corners in order to recover their original perspective. Instead, on a majority of trials children take a "beeline" to a particular corner (Huttenlocher, Lourneco, & Vasilyeva, 2006; Huttenlocher & Vasilyeva, 2003). This pattern implies that they rely upon a global representation of the shape of the space to infer their relation to a geometrically appropriate corner, regardless of which wall they are facing when they first open their eyes. Lee and Spelke (2011) also argue that a representation of global geometric layout is recruited during reorientation, rather than an image-matching approach of viewpoint specific "snapshots" (for review of this alternative theory see Shettleworth (2010)).

Given this account for how geometric reorientation is accomplished, it is clear that definition of the environment's overall global shape is a crucial. What defines the layout of a space? What contributes to its 'Euclidian shape,' to use Gallistel's term? Although it has been implicit to the discussion of geometry and reorientation over the years, I propose that environmental boundaries are a central and necessary component to define the shape of an environment. If I asked you to draw the shape of your office, you would most likely begin a floor plan by outlining the outer walls. Geometry has been described as a 'shrink-wrapped' representation that provides information about surface shape (Epstein, 2008). To take Epstein quite literally, we may turn to the work of artists Christo and Jeanne-Claude for a real-world example. Figure 2.2[2] shows one of their installations, which is a wrapping of the Reichstag building in polypropylene fabric. What remains is an impression of the geometry of the surface of the façade. Standing before this structure must have imparted a sense of imperious permanence to the viewer, who would have been struck by the immense solidity of the building's towering walls.

[2] Image source: http://annagravelle.wordpress.com/2010/01/22/christo-and-jeanne-claude/

Figure 2.2: The wrapped Reichstag in Berlin, Germany (1995, Cristo and Jeanne-Claude).

Boundaries, such as walls, fundamentally contribute to the geometric configuration of a space—their surfaces effectively define the outer limits of the present surround. Their salience and stability make them a useful cue for navigation. As reviewed above, the immediate and local boundaries of the pool apparatus are what rats use to represent location in the Morris water maze, as they are swimming to find the submerged platform where they can finally get some rest. Reorientation also presents a case when the navigating organism is under duress; no longer sure of what direction it's facing, it must re-establish the relationship between itself and the ambient space as quickly as possible. What does it turn to? Most primarily, the geometry of the space, to which environmental boundaries fundamentally contribute. Studies of controlled rearing (Chiandetti & Vallortigara, 2008; Gray et al., 2005) in geometrically uninformative circular environments have shown that chicks and fish are sensitive to the geometry of the walls of new rectangular enclosures, even though they have never seen an angle or linear adjacency of distinct walls before in their lives. Sensitivity to boundaries may be so crucial to successful navigation as to warrant evolutionary hard-wiring from birth.

The focus of this discussion is not to demonstrate to the reader the obvious point that boundaries exist in the world. Rather, the fact that reorienting organisms *depend* on the geometry of boundaries provides us with a method to answer the overarching question of what is a boundary, and what qualities are necessary to define it as such? Indeed, multiple studies have shown that when boundary structure is altered in different ways, geometric reorientation often fails. For example, rats and children do not reorient in accord with the shapes of two-dimensional (2D) patterns in the corners or on the walls of an enclosure (Cheng, 1986; Lourenco & Huttenlocher, 2007). Preschool children can reorient by the shape of an array marked by detached walls, but not detached corners or objects (Gouteux & Spelke, 2001). Studies with younger toddlers show that geometric relationships between identical landmarks are not used for reorientation (Lew, Foster & Bremner, 2006). These findings indicate that in order to be useful in specifying geometric information, boundaries must be made of extended three-dimensional (3D) surfaces. After having reviewed additional evidence, I will return to discuss the question of what constitutes a boundary in full.

Although data from spatial navigation tasks (e.g., reorientation, Morris water maze) provide compelling evidence for the importance of boundaries, it would seem that if boundaries truly are a fundamental cue, they should be uniquely represented by the brain areas known to be involved in spatial navigation. That is, the primacy of boundaries should be observable not only at the behavioral level, but also at the neural level. I next turn to discuss the relevant research.

Representation of boundaries in the brain

Neural bases of navigation

As our focus is on the use of boundaries in navigation, it is useful to initially provide

a general overview of the brain areas and structures involved in spatial function. Ungerleider and Mishkin (1982) first proposed that the visual system contains a division of labor for processing information about "what" in the ventral stream and "where" in the dorsal stream. Milner and Goodale (1995; 2008) have since proposed a revision to this division, where the ventral stream is responsible for processing object properties ("what"), and the dorsal stream is responsible for processing information relevant to visual-manual action ("how"). These two streams show numerous and complex interactions (Van Essen et al., 1992). More recent work has proposed further subdivisions (Kravitz et al., 2011b; 2013) and has also challenged a strict segregation of primary functions between what and where/how, demonstrating that representations associated with shape ("what") and location ("where") processing are present in both visual streams (Konen & Kastner, 2008; Kravitz, Kriegeskorte, & Baker, 2010; Sereno & Lehky, 2011; Zachariou et al., 2013).

Both the dorsal and ventral streams begin in primary visual cortex. The ventral stream then moves ventrally towards temporal areas, while the dorsal stream moves dorsally towards parietal and sensorimotor areas. The parietal lobe is involved in our ability to reach and grasp appropriately to objects located at a particular spatial location (Milner & Goodale, 2008), and within the parietal lobe, the intraparietal sulcus (IPS) has been linked to visually-guided motion and is also thought to play a role in visuospatial working memory (Todd & Marois, 2004). The parietal lobe is connected to the hippocampus and surrounding areas (cornu ammonis fields, dentate gyrus, and subicular complex) which are crucial for processing spatial navigation information (Aquirre & d'Esposito, 1999; Burgess et al., 1999; Epstein & Kanwisher, 1998; Squire et al., 2004).

Using virtual environments, neuroimaging studies of healthy adults have revealed a

complex neural network that supports navigation. This network includes the hippocampal and parahippocampal areas, frontal, posterior parietal, and occipital cortices, as well as the caudate nucleus (Aguirre et al., 1996; Burgess, 2002; Ekstrom et al., 2003; Hartley et al., 2003; Maguire et al., 1998; Orban et al., 2006; Peigneux et al., 2004).

Spatial encoding and retrieval of spatial memories relies upon the hippocampus (e.g., Burgess, 2008; Burgess et al., 2002; Maguire et al., 1998; Muller, 1996), located in the medial temporal lobe. The hippocampus plays a crucial role in allocentric spatial processing (Holdstock et al., 2000; Incisa della Rocchetta et al., 2004; King, Burgess, Vargha-Khadem, & O'Keefe, 2001; O'Keefe & Nadel, 1978), which enables the location of points within a framework that is independent of the organism's current heading and perspective. When the hippocampus is damaged, animals and humans have difficulty in spatial navigation and maze tasks (e.g., Bohbot et al., 2004; Maguire, Nannery, & Spiers, 2006; Rosenbaum et al., 2007; Spiers et al., 2001). Studies of patients with hippocampal lesions and functional neuroimaging work with neurologically healthy people have underlined the importance of the hippocampus in recognition memory tasks involving scene stimuli or spatial location/context (e.g., Bird, Vargha-Khadem, & Burgess, 2008; King et al., 2002; Ross & Slotnick, 2008; Taylor, Henson, & Graham, 2007). In rodents, studies using the Morris water maze have found that lesions restricted to as little as 25% of the dorsal hippocampus impair acquisition on the water maze and additional damage to the ventral region does not exacerbate the deficit (Moser et al., 1995). Lesions restricted to the ventral hippocampus have no effect on this behavior. In primates and humans, the posterior portions of the hippocampus correspond to the rodent dorsal hippocampus, while the anterior portions are analogous to the ventral hippocampus (Fanselow & Dong, 2010). It is interesting to note that humans proficient in

spatial navigation (i.e., London taxi drivers) show increased posterior but decreased anterior hippocampal volume (Maguire et al., 2000).

In contrast to allocentric-based representations of the environment, organisms may also rely upon an alternative type of representation that derives from route learning. When following the same route over and over again, a representation of the sequence of bodily movements may develop (Hartley et al., 2003). This response-based type of navigation relies upon the striatal complex and in particular the caudate nucleus (Hartley et al., 2003; Iaria et al., 2003; Orban et al., 2006; Packard & Knowlton, 2002), which encodes procedural knowledge about what action to take at decision points when following a route (e.g., turn right at the grocery store).

Studies have shown that activation in the response-based vs. allocentric-based systems (Packard & McGaugh, 1996) varies across individuals, depending on whether a space-based or a response-based navigational strategy is used (Furman et al., 2014; Hartley et al., 2003; Iaria et al., 2003). Furthermore, volumetry studies indicate that the hippocampus is larger and the caudate smaller in participants who use a spatial rather than a response-based strategy to recall locations in an 8-arm virtual maze (Bohbot et al., 2007). Size of the right posterior hippocampus has also been shown to predict the ability to make inferences about the relative positions of buildings on a familiar college campus (Schinazi et al., 2013).

Neural representation of boundaries

Of the neural structures and regions described above, are some specifically involved in navigation by environmental boundaries? Data gathered by Doeller, King and Burgess (2008) using a virtual reality environment suggest that there are two separable systems in support of navigation by boundaries vs. navigation by landmarks. The virtual environment

used in this study contained an intra-maze landmark (traffic cone), a circular boundary, and extra-maze orientation cues (mountains, which were uninformative in terms of spatial location). Participants learned the locations of objects by collecting and then returning them to their original position over the course of multiple trials. The locations of the boundary and landmark were intermittently changed, and the locations of some objects were paired with the cue of the boundary, while others were paired with the cue of the landmark. It was found that right posterior hippocampal activation reflected learning and remembering of boundary-related locations, and right dorsal activation reflected learning and remembering of landmark-related locations. Iaria et al. (2003) observed that when subjects encoded locations using distal landmarks around a virtual radial maze, they showed increased hippocampal activation relative to a visuomotor control condition. Hippocampal activation has also been shown to increase parametrically with the number of enclosing boundaries in mental scene images, which participants were asked to recall after studying aerial views of different environments (Bird et al., 2010). Collectively, these findings point to the hippocampus as a central structure involved in navigation and representation of spatial location by boundaries.

Given our discussion of the fundamental contribution of boundaries to environmental geometry, are the same areas implicated in navigation by boundaries also involved in reorientation? Only a few neuroimaging studies to date have investigated the brain areas involved when people are forced to reorient themselves. Also using virtual reality, Sutton et al. (2010) created three experimental conditions: a rectangular room with light gray identical walls (Geometry), a room of the same shape but with one short wall that was colored red (Feature + Geometry), or a square shaped room with three light gray walls and one red wall (Feature, no geometry in this case because this room was square shaped, thus rendering

geometric information symmetrical and uninformative for locating a hidden target). When participants retrieved concealed objects in the two environments that included the feature of the red wall, the bilateral hippocampal and left parahippocampal cortex regions were found to be more engaged than when the room was entirely gray (the Geometry condition). Consistent with the findings of Doeller et al. (2008), this pattern suggests that the hippocampus is engaged in processing cues that are part of the environment's boundary.

The studies by Doeller et al. (2008) and Sutton et al. (2010) provide insight to the neural bases of the use of boundaries in active navigation tasks. However, are there certain areas of the visual system that are specifically dedicated to processing the spatial information of our environment, before we begin to act upon it? Are boundaries uniquely encoded as aspects of the scene view that meets our eyes when we first survey the space around us? If so, this would suggest that boundaries are not only useful cues when we act upon an environment to travel through it, but also are primary factors in the visual representation of scenes.

Representation of boundaries in scene-selective visual areas

In this section I discuss three high-level visual areas of the brain that play a role in the processing of scenes (Figure 2.3): the parahippocampal place area (PPA, Aguirre et al., 1996; Epstein & Kanwisher, 1998) the retrosplenial complex (RSC, Epstein 2008; Maguire et al., 1997; 1998), and the transverse occipital sulcus (TOS, Dilks et al., 2011; Grill- Spector, 2003; Hasson et al., 2003; MacEvoy & Epstein, 2007; Nakamura et al., 2000). In fMRI studies, PPA, RSC, and TOS are selectively sensitive to scenes and are functionally defined by contrasting activity for images of real-world scenes vs. images of objects.

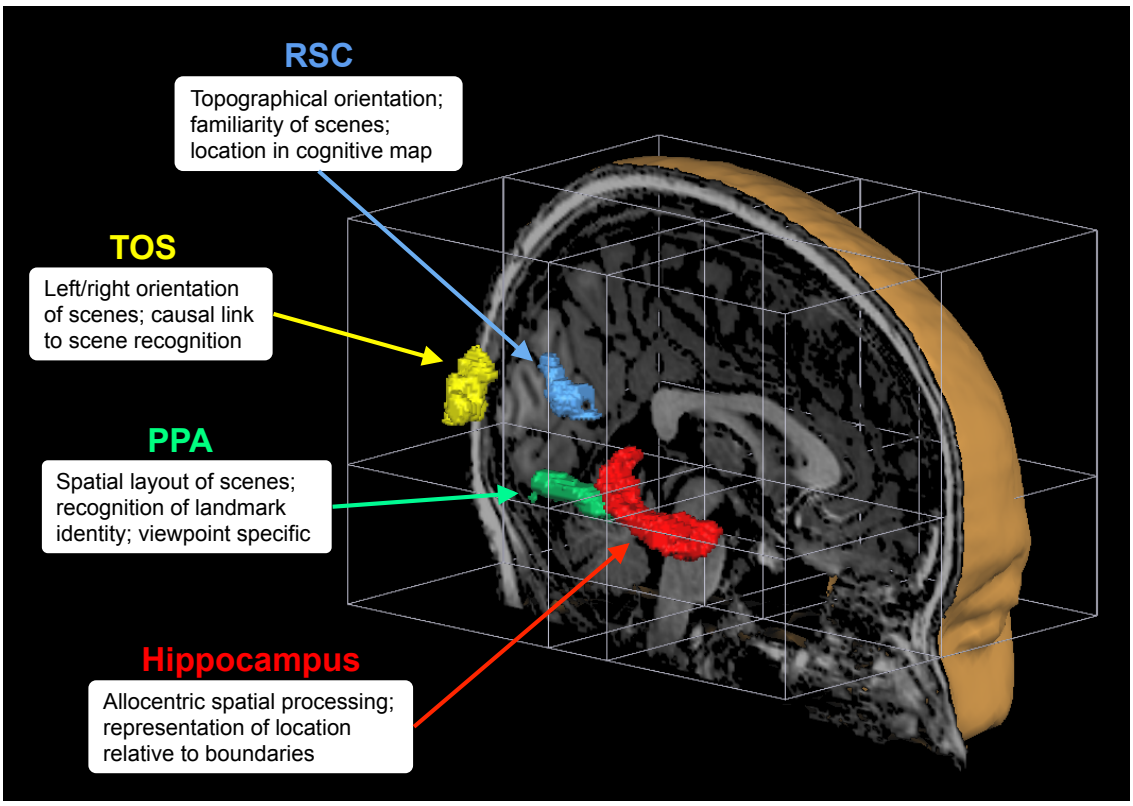

Figure 2.3: Brain areas involved in scene processing.

A growing body of work has explored properties of the scene-selective areas of PPA and RSC. I will first focus on distinctions between these two areas. PPA is located along the ventral stream, at the boundary between posterior parahippocampal cortex and the anterior lingual gyrus. RSC is an intermediate area along the parieto-medial temporal pathway (Kravitz, et al., 2013), in the retrosplenial cortex/posterior cingulate medial parietal region, near the point where the calcarine sulcus joins the parietal-occipital sulcus. The parahippocampal and retrosplenial cortices are active during human navigation (Ghaem et al., 1997; Ino et al., 2002; Maguire et al., 1997; 1998; Rosenbaum, 2004; Spiers & Maguire, 2006), and also respond strongly during passive viewing of navigationally relevant visual stimuli, such as scenes and buildings (Aguirre, Zarahn, & D'Esposito, 1998; Epstein & Kanwisher, 1998; Hasson et al., 2003; Nakamura et al., 2000).

Damage to the PPA and RSC often results in deficits in wayfinding (Aguirre, & D'Esposito, 1999; Aggleton & Vann, 2004; Alsaadi et al., 2000; Greene, Donders & Thotis, 2006; Katayama, et al., 1999; Osawa, Maeshima, & Kunishio, 2008), but the specific type of resulting deficit highlights important differences between the two regions. Individuals who have damage to RSC are often able to recognize buildings and landmarks, but they are unable to use them to infer direction and orientation. One study describes the experience of a patient soon after suffering a stroke to the region; "he could recognize buildings and the landscape and therefore understand where he was, but the landmarks that he recognized did not provoke directional information about any other places with respect to those landmarks. Consequently, he could not determine which direction to proceed." (Ino et al., 2007). Patients who experience damage to the PPA as a result of stroke often report the converse, where they cannot identify large topographical entities (streets, buildings, intersections, etc.) (Barrash et al., 2000), but their understanding of the spatial relationships between different locations is often preserved (i.e., they are able to draw maps of the route they would take between different locations (Mendez & Cherrier 2003; Takahashi & Kawamura, 2002)). These contrasting findings suggest that RSC is involved with integration of landmarks into a global spatial framework, while the PPA is involved in recognition of the identity of specific landmarks. In addition to patient work, the study of individuals with genetic disorders who also show abnormalities in these scene-selective regions may reveal further insight (to be explored in the current thesis research).

Neuroimaging research with healthy adults provides further evidence of distinct roles that are played by the PPA and RSC in scene recognition. Epstein and colleagues (Epstein, Parker, & Feiler, 2007) showed college students images of their college campus and also

those from other campuses. Students were asked to either report the location of the image (Is this picture east or west of 37th street?), the orientation of the image (Is this picture taken from a camera facing east or west?), or the familiarity of the image (Was this photograph taken on the Penn campus?). The response of RSC was modulated by the type of information that was retrieved, showing the strongest response in the location task, followed by the orientation task, and also showed a stronger response to familiar campus images over unfamiliar images (Figure 2.4). In contrast, activity of the PPA did not depend upon the retrieval task. In another experiment using virtual reality, multivoxel patterns in RSC were shown to code for both imagined location and facing direction, based upon fixed elements in the local environment (Marchette et al., 2014). These results indicate a primary role of the PPA in scene perception and a primary role of RSC in topographical orientation and memory retrieval. In additional support of these complementary roles, Park and Chun (2009) manipulated panoramic scene images to find that the PPA is viewpoint specific, treating successive changes in viewpoint of the same scene as unique. In contrast, RSC was found to be viewpoint invariant across multiple views of the same scene, integrating across similar scenes that were continuously presented. Together with the deficits revealed by patient work, these collective findings indicate that the PPA is concerned with representation of local physical scene structure, while RSC is concerned with situating the scene within the broader spatial environment (Epstein, 2008).

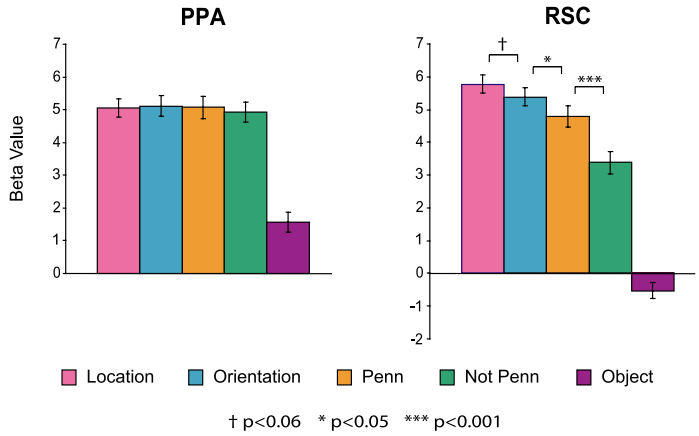

Figure 2.4: fMRI response in the PPA and RSC in the experiment conducted by Epstein and colleagues. The PPA showed no effect of retrieval task or familiarity, responding equally strongly in all four conditions in which scenes were shown (the Object condition was included as a baseline, in which participants reported whether an object was a vehicle or not). RSC response was affected by both retrieval task and familiarity (Epstein et al., 2007).

fMRI studies have revealed a third region that is engaged in visual scene processing, located around the transverse occipital sulcus (Dilks et al., 2011; Grill-Spector, 2003; Hasson et al., 2003; MacEvoy & Epstein, 2007; Nakamura et al., 2000). In the literature this region is known historically as TOS (Grill-Spector, 2013), and more recently has been re-named as the "occipital place area" (OPA, Dilks et al., 2013). To date the characterization of this area's role in scene processing is less well-specified than that of the PPA and RSC, but a recent study has shown that it is sensitive to the left-right orientation of scenes, but not objects (Dilks et al., 2011). Using transcranial magnetic stimulation (TMS), research has also highlighted a causal role of TOS/OPA in scene discrimination and categorization accuracy (Dilks et al., 2013).

The way in which inputs from these various regions connect to one another across the scene network is a topic of ongoing research. Functional connectivity analyses show that parahippocampal and retrosplenial regions have strong functional connectivity to the hippocampus and other medial temporal regions, such as the entorhinal and perihinal cortices

(Rauchs et al., 2008; Summerfield et al., 2010). Connectivity results in humans, using both diffusion tensor imaging (DTI) and fMRI, have shown that the parahippocampal region is connected to occipital visual cortex (Kim & Kim, 2005; Libby et al., 2012; Rushworth et al., 2006) as well as RSC and posterior parietal cortex (Caspers et al., 2011; Kahn et al., 2008; Libby et al., 2012; Rushworth et al., 2006; Uddin et al., 2010). Baldassano et al. (2013) have further demonstrated distinct connectivity patterns between anterior vs. posterior PPA, with anterior PPA more strongly connected to regions in the default mode network (including the parieto-medial temporal pathway, likely more involved in memory and scene context) and posterior PPA more strongly connected to occipital visual regions (likely more involved in the processing of low-level visual features and object shape). Because TOS/OPA is situated more posterior than PPA or RSC, Dilks et al. (2013) speculate that this region is involved in earlier stages of scene processing.

Representation of boundaries at the neuronal level

The discussion above focuses on cortical regions and their representation of boundaries. If boundaries truly are of utmost importance in navigation and representation of spatial location, they may warrant not only specific regions dedicated to their processing, but also precisely dedicated mechanisms at the cellular level. Looking this closely at the mechanisms underlying navigation requires using single- or multi-unit cellular recordings. Studies using these methods in animals have begun to reveal how navigation is implemented at the neuronal level, identifying several classes of cells that encode spatial quantities useful for navigation. Together with place cells in the hippocampus (which fire when the animal moves through a particular location in space (Moser, Kropf, & Moser, 2008; O'Keefe & Dostrovsky, 1971; O'Keefe & Burgess, 2005; O'Keefe & Nadel, 1978)), head direction cells

(which fire when the animal is facing a certain direction (Ranck, 1986; Sargolini et al., 2006; Stackman & Taube, 1997; Taube, 2007; Taube, Muller, & Ranck, 1990)), and grid cells in entorhinal cortex (whose localized firing fields form a regular triangular/hexagonal pattern across the environment (Fyhn et al., 2004; Hafting et al., 2005; Moser, Kropf, & Moser, 2008; Sargolini et al., 2006)), boundary vector cells (BVCs) and border cells form a network of neurons that collectively encode an animal's current position in the environment.

As indicated by their names, BVCs and border cells are of particular relevance to our focus on the representation of environmental boundaries at the neuronal level. The existence of BVCs and their input to place cells was theoretically proposed before their actual discovery (Burgess et al., 2000; Hartley et al., 2000; O'Keefe & Burgess, 1996). By recording from subicular pyramidal cells in the hippocampal formation, Lever and colleagues (Barry et al., 2006; Lever et al., 2009) discovered cells whose spatial firing characteristics were consistent with those of the proposed BVCs; firing whenever an environmental boundary intersected a receptive field located at a specific distance from the rat in a specific allocentric direction. The firing of a BVC depends solely on the rat's location relative to the boundary—firing is independent of the rat's heading direction and nonspatial properties, such as the color of the boundary. As discussed above, featural information (e.g., color) does not bear relevance to the geometric properties of an environment. Thus, in their chief responsibility of encoding boundaries, it would not be efficient for the response BVCs to be modulated by changes in non-geometric properties such as color.

BVCs fire at specific fixed distances from a boundary. The preferred firing distance for a particular BVC could be close to a boundary, or far away from it. In contrast, border cells, found in the entorhinal cortex and the parasubiculum, fire whenever an animal is close

to or at a boundary in the environment (Solstad, et al., 2008). They are speculated to be a special case of BVCs (Gallistel & Matzel, 2013). Together, the existence of BVCs and border cells signify a specific and specialized neural mechanism dedicated to encoding environmental boundaries. This mechanism is present early in the developmental timeline (by the third week of a rat's life (Wills et al., 2010)), and is at work even when the animal is deprived of visual input. Lever and colleagues have shown that once a rat is familiar with an enclosure, BVCs will continue to fire in absolute darkness, just as they had when the lights were turned on (Lever et al., 2009). It is yet to be determined how long the pattern of these firing rates will remain consistent, yet the fact that they are not dependent on purely visual information underscores the importance of their input for the navigating organism. Even in the dark, we want to try to track how close we are to the boundaries of a room to avoid the unfortunate consequence of bumping into a wall.

The flexibility of BVCs is demonstrated by their response to enclosures of different geometric shapes. The boundaries of our local environment may dramatically change in shape and size as we move from one location to the next, and thus it is of utmost importance to be adaptable to these changes. Indeed, in each of the four environments shown in Figure 2.5 (2.5.A square, 2.5.B cylinder, 2.5.C diamond, and 2.5.D square with an additional boundary inserted), Lever et al. (2009) found that BVC firing fields were consistently a function of distance and allocentric direction to the boundaries of the local environment, regardless of the shape of the enclosure that the rat happened to be in at the time. If an additional boundary was inserted at the appropriately preferred orientation (Figure 2.5.D), the firing field of the BVC doubled to reflect the presence of this new boundary.

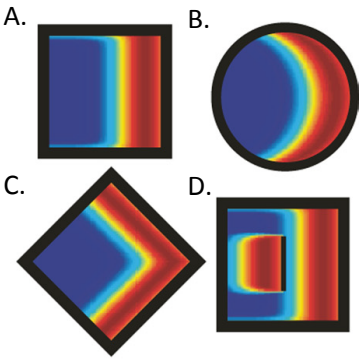

Figure 2.5: Predicted firing fields for a BVC (Lever et al., (2009), adapted from Hartley et al. (2000).

Border cells also show spontaneous remapping to transformations of the geometry of a rat's enclosure. Savelli, Yoganarasimha and Knierim (2008) have shown that manipulation of local boundaries can exert powerful influence on the spatial firing patterns of border cells. In their study, rats foraged in a small square box for 6 minutes. After 6 minutes, without removing the rat from the enclosure, the walls of the small box were quickly removed, and the rat was left free to continue foraging in the whole area enclosed by a larger box. Cells were identified that fired along a particular wall or corner in both spaces, regardless of whether the enclosure was large or small. This demonstrates spontaneous remapping to accurately reflect the boundaries of the present environment.

The study of BVCs and borders cells suggest the existence of neuronal correlates to the sensitivity to boundaries that we see reflected in behavioral tasks such as the Morris water maze and the reorientation paradigm. Many different accounts have been proposed to model the specific way in which inputs from grid cells, head direction cells, BVCs, and border cells are integrated to form a coherent representation of the environment. Properties reflected by BVCs might play a role in binding the path-integration-based grid cell representation to the boundaries of a given environment (Savelli et al., 2008). With this information, grid cell firing may then give rise to place cell firing, via hardwired synaptic

weights (Hayman & Jeffery, 2008; Solstad et al., 2006), effective Fourier synthesis (de Almedia et al., 2009; O'Keefe & Burgess, 2005), a Hebbian learning rule (Hasselmo, 2009; Savelli & Knierim, 2010), and/or competitive network interactions (Rolls et al., 2006; Si & Treves, 2009). Others argue that place cell firing is *primarily* driven by environmental sensitivity inputs from boundary/border cells (e.g., Barry et al, 2006; Bush et al., 2014; Lever et al., 2009), given the observation that the position of place fields in altered environments can be strongly predicted by their position relative to previous boundaries, and that additional place fields often develop in the same relative position when an additional boundary is placed in a familiar environment (Hartley et al. 2000; O'Keefe & Burgess, 1996). Also in support of this view is the fact that adult-like boundary cell activity develops much earlier than grid cell responses (Wills et al., 2010). Although we do not yet have a model that all agree on, it is clear that one of the primary functions of the neuronal network subserving navigation is to provide the animal with information about environmental boundaries at various distances and directions. Boundaries are of paramount importance in representing an animal's current position in the environment.

What constitutes a boundary?

The literature reviewed above demonstrates that boundaries are an important cue for navigation (especially geometric reorientation), are encoded by scene-selective visual areas, and even have specific types of cells devoted to their processing. However, it remains unclear what factors truly characterize a boundary as such.

Does an extended surface only constitute an effective boundary once it imposes a limit on our movement and/or vision? It has long been noted in the field that boundaries may be defined in terms of their functional affordance (Kosslyn & Pick, 1974). In their discussion

of the role that boundaries play in the formation of cognitive maps, Newcombe and Liben note that "barriers…prohibit direct travel between particular points. If traveled (functional) distance is important for individuals' cognitive representation of space, then the distances between two points may be exaggerated when they have been separated by barriers" (Newcombe & Liben, 1982). Evidence for encoding of boundaries that is dependent upon their functional significance may be found in research on BVCs. Although these cells were originally discovered to fire in response to the wall boundaries of a rat's enclosure (Lever et al., 2009), further work on drop boundaries (where rats are placed on an elevated platform) has shown that drops elicit field repetition in BVCs in the same way as upright barriers. This indicates that BVCs treat drops similarly to walls. As walls and drop edges have very different sensory properties, similar coding of walls and drops highlight a specialized coding for environmental boundaries *per se* (Stewart et al., 2013), irrespective of sensory input. Whether it be a drop off a cliff or an un-scalable smooth wall, both boundaries are equivalent in their imposition of an absolute limit to future navigation. When we come across boundaries of this kind, it is often the best decision to alter our path and walk in a different direction.

And yet, other data seem to tell a very different story, one in which boundaries are not represented in terms of whether they pose a significant hindrance to navigation. For example, BVC firing anchors and shows field repetition to the limits of the three rectangular platforms shown in Figure 2.6. Rats are able to cross the 10 cm gaps between these platforms with ease (Stewart et al., 2013). This suggests that a boundary *need not present an absolute impediment to movement* to be an effective boundary stimulus.

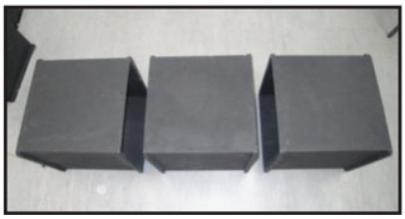

Figure 2.6: Platforms used by Stewart et al. (2013), which were separated by 10 cm gaps.

A series of studies examining the reorientation abilities of preschoolers (Lee & Spelke, 2008; 2011) further demonstrate that the effectiveness of a boundary does not necessarily depend upon its direct navigational relevance. For example, Lee and Spelke (2011) used a rectangular array defined by four columns, which were connected together by a cord (Figure 2.7.A). Even though this manipulation effectively constrained children's movement, they were unable to reorient geometrically (i.e., they searched the four corners of the array at random). This indicates that functional limitation to movement, in and of itself, does not constitute an effective boundary. In contrast, children do reorient successfully by a slight 3D curb structure that extends only 2 cm from the ground (Figure 2.7.B). In this curb array, children searched more frequently are the correct corner and its rotational equivalent. Rather than overall functional relevance, these findings highlight children's exceptional sensitivity to boundaries that create very subtle alterations in surface layout geometry. These types of boundaries do not dramatically impede motion or vision. Crucially however, children's acute sensitivity is tied to boundaries that introduce changes in 3D structure (even if exceptionally slight), as they do not reorient geometrically in 2D arrays defined by tape on the floor (Lee & Spelke, 2008) or a flat black mat (Figure 2.7.C) (Lee & Spelke, 2011). Children's difficulty in using 2D boundaries echoes the performance of adults tested by Hamilton et al. (2009) in the virtual Morris water maze. In both cases, participants had

difficulty navigating accurately when boundaries were rendered flush to the surface of the navigable space (either the virtual water of the pool or the floor area inside the lines of tape).

Figure 2.7: Reorientation arrays used by Lee & Spelke (2011). A) Free standing pillars connected by a cord, B) 2 cm curb, C) 2D flat black mat.

Collectively, data on BVC response patterns and the reorientation of children indicate that the qualifying criteria for a boundary is more nuanced than absolute functional affordance. However, all of the effective types of boundaries discussed thus far (even 2 cm curbs and 10 cm gaps) do pose *behavioral consequences*. For example, a rat would need to be mindful of the 10 cm gap to make the short jump and avoid falling between the platforms, and even an adult may want to heighten her stride to prevent herself from tripping over a 2 cm curb. Although they have very different sensory properties, what both a 10 cm gap and a 2 cm curb have in common is that they alter the *geometry* of the navigable surface. This is why they present consequences to behavior, even if very minor. 2D forms, which reorienting children and have difficulty using, do not introduce changes in geometry and thus do not pose behavioral consequences.

These data suggest that a boundary need not pose an absolute functional limit to navigation, but at the same time is far more effective when it introduces a *change in the geometric relationship* between the surface of the ground and the surface of the boundary. In Gallistel's own words, a geometric property of a surface "is a property it possesses by virtue of its position relative to other surfaces…within the same space." (Gallistel, 1990, p. 212).

Although Gallistel intended for his definition to apply to geometric relationships of any kind, it quite accurately fits the data reviewed thus far on what qualifies as an effective boundary: it must present a change in the *geometry* of the navigable surface.[3]

A qualification is that the change in geometry must be *continuous* and extend along the navigable surface. Isolated and individual objects do not meet this criterion, and research shows that these objects are not useful to children in reorientation. Three- and four-year-olds cannot use isolated elements to define geometric information (Goutex & Spelke, 2001), to locate the middle of an array (MacDonald, Spetch, Kelly, & Cheng, 2004), or to locate one element in terms of its relations to other elements (Uttal et al., 2001). Furthermore, children do not reorient geometrically in arrays where detached corners or objects are arranged in a rectangular shape (Gouteux & Spelke, 2001; Lew, Foster & Bremner, 2006). These data suggest that in order for geometric information to be informative for reorientation, it must not be in the form of an isolated object. Rather, it must extend along the navigable surface for a significant distance. What qualifies as a "significant distance" is difficult to define, as the transition from when something changes from a discrete object to a boundary is yet to be clarified. This in part depends on the size of the navigating organism (to offer an exaggerated example: a pebble may not be noticeable to us, but would present a functionally limiting and dramatic boundary to an ant who would have to alter his path to make his way around it).

[3] Degrees of behavioral relevance and geometry often go hand in hand for the types of boundaries that we encounter in the real world. But in some cases, these factors exist independently. The edge of a lake, where water meets solid ground, is an instance of a boundary that holds great behavioral consequence without an appreciable change in geometry. Gallistel's discussion of the material of a surface is relevant to this example, "It seems likely that phase transitions—the loci of changes from liquid to gaseous to solid forms of materials—are in important aspect of material reality for most animals and the perception of surfaces is, in appreciable measure at least, the perception of these transitions in material phase." (Gallistel, 1990, p. 213). Although it is left to be pursued by future research, I hypothesize that representation of the navigational consequences of surface material is supported by neural mechanisms that are in some ways separable from those that are specifically devoted to geometric boundaries.

Do high-level scene selective visual areas represent boundaries in ways that conform to the criteria I have proposed thus far? This question was explored within the healthy adult population in my previous research (Ferrara & Park, 2014). Lee & Spelke's (2008; 2011) findings with young children demonstrate that a very slight amount of vertical boundary information is sufficient to trigger geometric reorientation. This indicates that vertical structure is a core aspect of boundary representation. If this feature truly is core, we predicted that there may exist a neural signature in the adult brain that differentiates between the amount of vertical boundary cue present in a scene. Furthermore, it is possible that this differentiation could be so finely tuned as to mirror the striking behavioral reorientation results that have been found for young children. Specifically, we hypothesized that scene selective areas may show different responses to a slight amount of 3D vertical structure in comparison to a 2D flat mat. If the slight 3D vertical cue of a curb structure makes a difference, then we expected to see a scene area that is sensitive to the slight addition of the curb on top of the mat, even though these two conditions appear quite visually similar to one other (Figure 2.8). On the other hand, a slight vertical cue may not be sufficient, and a full wall-like structure that has preventative consequences for the locomotion of the viewer may be required. In this case, if the representation of boundaries is driven by their functional affordance, we predicted that patterns of activity would be quite similar for the mat and the curb, and only distinguishable for a condition that presented full wall boundaries.

To test these predictions, we used fMRI to measure the neural response to visual stimuli that portray three types of cues: a Mat condition in which no vertical structure is present, a Curb condition where there is a very small addition of 3D structure (modeled off

the results of Lee and Spelke (2008; 2011)), and a Wall condition which resembles a typical indoor space (Figure 2.8).

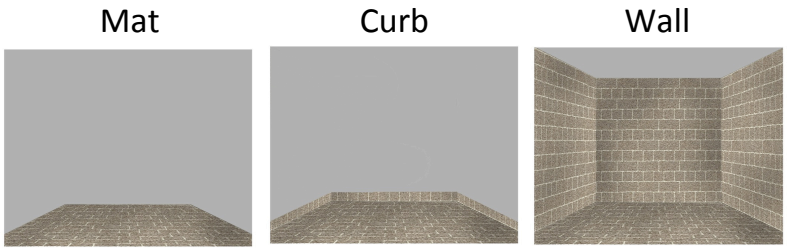

Figure 2.8: Examples of the Mat, Curb, and Wall conditions used by Ferrara & Park (2014).

Measures of univariate response and multivoxel pattern analysis (MVPA) revealed that activity of the PPA showed significantly different levels of response that increased from the Mat, to the Curb, to the Wall (Figure 2.9.A). In contrast, activity of the RSC did not distinguish between the Mat and the Curb, and only showed a significantly different response to the full Wall condition (Figure 2.9.B). These results indicate that the PPA and RSC have different sensitivities to different types of boundary cues—while PPA is sensitive to very slight manipulations of 3D structure (i.e., the difference between the Mat and Curb), RSC is not sensitive to minimal 3D structure and requires the strong vertical cue of the wall. The fine-grained sensitivity of the PPA in discriminating the Mat vs. the Curb reflects the findings of Lee & Spelke (2008; 2011), which demonstrate that the reorientation mechanism of young children is finely tuned to detect a very small amount of 3D vertical structure.

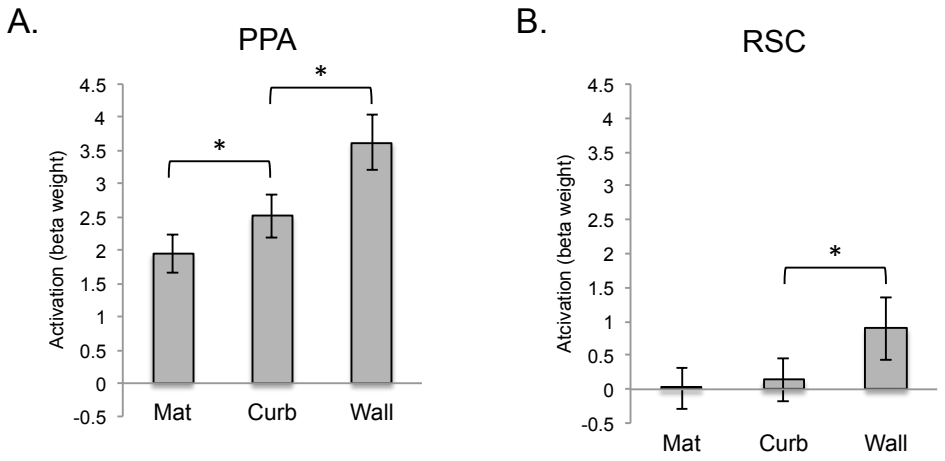

Figure 2.9: A) Beta weights for the PPA for each of the three boundary conditions (Mat, Curb, and Wall). B) Beta weights for RSC for each of the three boundary conditions. Error bars represent +/- standard error of the mean. Asterisks indicate significant difference between conditions, $p < .025$ (Ferrara & Park, 2014).

Why did RSC not distinguish between the Mat and Curb and responded strongly to only the Wall? One possibility that Ferrara & Park (2014) tested is that RSC may represent boundaries in terms of their functional affordance. The Mat and Curb are boundaries that are easily crossable, while the Wall is not. As discussed earlier, boundaries may be characterized in terms of their imposed limitations to locomotion or vision (Lee & Spelke, 2008; Lever et al., 2009; Newcombe & Liben, 1982). To pursue this hypothesis further, we used stimuli that incrementally varied the height of the boundary on a more fine-grained scale (Figure 2.10).

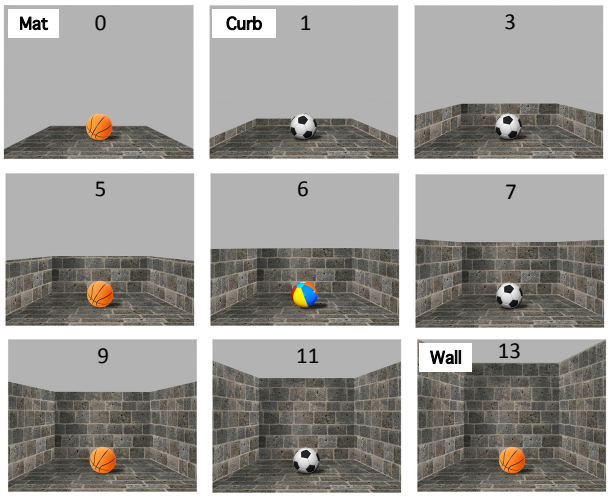

Figure 2.10: Nine boundary heights tested (Mat, Curb, and Wall conditions included for the purpose of replicating previous results) (Ferrara & Park, 2014).

We predicted that if RSC responds to the functional affordance of a boundary, it would demonstrate a modulation in response that is driven by a functional cut-off point—the point at which the boundary changes from something that the viewer could easily traverse, to something that limits the functional affordance of the scene. Analysis of RSC's univariate response to each of the nine conditions revealed only one significant pairwise comparison; that between boundary heights 5 and 6 (Figure 2.10). Even though the pixel amount is kept at a constant increase from one boundary condition to the next, the response of RSC reflects a categorical difference between heights 5 and 6. This difference is mirrored in the behavioral judgments that people make. We asked participants to decide whether a boundary of a particular height was easy to cross, (like a small curb), or difficult to cross (like a full wall). We found the consistent tipping point between these two categories to occur between heights 5 and 6. This congruence between behavioral and neural response suggests that the representation of boundaries by RSC is driven by functional affordance. This finding supplements other studies in the literature, which suggest that RSC plays a role in

representing the navigability of scene (Park, Levine & Dunne, 2013). Collectively, our research reveals that RSC and PPA represent boundaries in qualitatively different ways; while RSC encodes the functional consequences of a given boundary, the PPA is finely tuned to detect the 3D vertical extent of a boundary.

A final qualification in our discussion of what constitutes a boundary is that it must present a continuous change in geometry that is *grounded* to the navigable surface; the boundary must extend from the ground up. Behavioral consequences such as tripping over a small curb, or having to jump between two separated platforms (as rats did in the study by Stewart et al. (2013)), arise from the way that one traverses the ground surface. As rats and ourselves are not aerial species, it follows that effective boundary cues are tied to the ground, just as our navigation is tied to the ground. Several pieces of evidence support this criterion. First, Lee & Spelke (2011) found that children did not reorient geometrically in an array of columns that were connected at their midpoints by a cord. The continuous boundary, in this case, was suspended in the air.[4] A second piece of evidence comes from our own previous work (Ferrara & Park, 2014). We noticed that the PPA showed a disproportionately large response to the Curb condition—the increase in activity from the Curb to the Mat was nearly as great as the increase from the Curb to the full Wall (Figure 2.9.A). We ran a follow-up study with the same boundary stimuli, but this time turned them upside down. The PPA did not show the same graduated step-wise pattern of response for these inverted stimuli as it had for the right-side up images (Figure 2.11). Now, its responses to the Mat and the Curb were no longer different from one another. These data suggest that the presence of *grounded* minimal vertical structure plays a critical role in the representation of boundaries by the PPA.

[4] A construction of this type would most likely present a salient boundary to avian species, for whom landmarks connected by cords (i.e., telephone poles) are important things to be aware of while flying through the air.

Inverting the images disrupted the ecological validity of boundaries that typically rise from the ground up, and consequently disrupted the PPA's exceptional sensitivity to the slight vertical structure of the Curb condition.

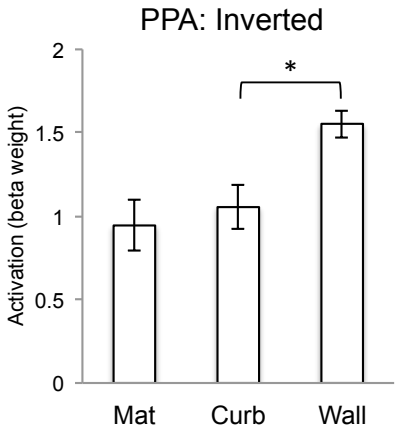

Figure 2.11: A) Beta weights for the PPA for each of the three inverted boundary conditions. Error bars represent +/- standard error of the mean. Asterisk indicates significant difference between conditions, $p < .025$ (Ferrara & Park, 2014).

Now that we have reviewed the relevant literature on both the neural representation of boundaries and their use in navigation by adults, children, and animals, we may begin to formulate a checklist to identify what factors constitute an effective boundary.

What constitutes a boundary? A checklist

1. A boundary prescribes the limits of the *local* navigable space.

The work of Hamilton et al. (2007; 2009) with rats and humans in the Morris water maze demonstrates that local boundaries are relied upon more heavily than distal boundaries to represent spatial location. This makes intuitive sense—imagine trying to represent your current position in space by referencing a boundary far away in the distance, say the boundary on the horizon where some mountains meet the sky. You may travel several meters, and yet, in relation to this boundary that is far removed from your own person, your relative position has changed little. Gallistel notes that "a place is a place by virtue of the

geometric relations it bears to the surfaces in the animal's *behavioral space*" (Gallistel, 1990, p. 216, emphasis added). Behavioral space refers to the area that the organism has the potential to occupy in the near future. The presence of a boundary in this behavioral space presents a cue that is used in navigation and is also represented in scene-selective areas at the neural level.

2. A boundary introduces an alteration to *geometry*.

Boundaries fundamentally contribute to the "shrink-wrapped" geometry of a scene. However, the geometric contribution of a boundary does not have to be strikingly salient in order for it to be effective. Reorienting children are impressively sensitive to boundaries that create very slight alterations in surface layout geometry (Lee & Spelke 2008; 2011). When the boundary is changed to a 2D form however, children cannot reorient geometrically. Their acute sensitivity is tied to 3D structure only, and no matter how salient the contrast imposed by the 2D boundary (Lee & Spelke, 2011), they will fail to spontaneously use the geometric information it conveys. This indicates that 3D changes in geometry form boundary cues that are privileged input for the reorientation mechanism. Yet it is possible that sensitivity to 2D boundaries in this paradigm may be observed in older children, as the underlying representation of boundaries may become more flexible and abstract as development progresses (to be explored in this thesis). At its core however, I maintain that the evidence reviewed above strongly suggests that the essence of a boundary is tied to the change it introduces to geometry in 3D space. Note that the change may be either positive or negative, as both the addition (walls) and subtraction (drops) of geometric structure anchors BVC firing.

3. A boundary is *continuous* along a broadly horizontal planar surface.

A single isolated object is not sufficient to qualify as a boundary. An object may serve as a landmark to indirectly represent spatial location, but simply because something qualifies as a landmark does not mean that it also qualifies as a boundary. To return to Gallistel's focus on "behavioral space," I propose that a boundary extends along a significant portion of behavioral space, whereas a landmark takes up only one circumscribed area of behavioral space. As noted above, it is difficult to provide a universal benchmark to determine when a change in geometry has extended along a significant portion of your behavioral space (i.e., when it is has become a boundary). This benchmark is likely at varying points across species, which operate under different modes of navigation.

4. A boundary *rises from the ground up*.

For organisms whose navigation is primarily tied to the ground, changes in geometry must also occur from the ground up in order to qualify as boundaries. Children do not reorient geometrically in arrays defined by a suspended cord (Lee & Spelke, 2011). Although the cord functionally blocks children from stepping outside the array, this does not trigger geometric reorientation. Thus, functional relevance alone is not sufficient to qualify as a boundary. If continuous 3D structure is not tied to the navigable surface, it does not form an effective boundary.[5] In further support of this criteria, our own research has revealed that sensitivity of the PPA to 3D vertical structure is only observable when the structure rises from the ground up (Ferrara & Park, 2014).

5. A boundary poses *behavioral consequences* to navigation.

[5] Admittedly, there is some gray area here as well. Imagine it were possible to create an array in which four walls floated just a few centimeters above the surface of the floor. Would children reorient geometrically in this space? Would BVCs respond to the floating walls as boundaries? It is difficult to say, but either way, it is notable that only a minimal amount of vertical structure that is *connected* to the ground surface is sufficient to both elicit consistent BVC firing and trigger geometric reorientation by children, while a suspended minimal element (i.e., a cord) is not.

This section began by discussing the possibility that boundaries are defined by the dramatic limit they place on future navigation—when you come to a boundary, you can go no further (or you find a door to walk through it). However, further evidence suggests that effective boundaries present some type of behavioral consequence to navigation, whether it be slight or absolute. You may not even be aware of the fact that you heightened your stride to cross a small curb on the ground, but this effect qualifies as a behavioral consequence of the change in geometry introduced by the curb. BVCs fire in response to boundaries that impose slight behavioral consequences (a small gap between surfaces (Stewart et al., 2013), or a small ridge (Lever et al., 2009)). Additionally, our own previous research indicates that RSC represents boundaries in terms of categorical differences in behavioral consequence—whether they are easy or difficult to cross (Ferrara & Park, 2014).

In embodying each of these five factors, boundaries contribute to the geometric shape of an organism's behavioral space. A large body of research has documented that geometry is the primary form of input that an organism will use when it needs to reestablish the relationship between its own heading and the external environment (i.e., reorient itself). Our own neuroimaging findings (Ferrara & Park, 2014) suggest a connection between the finely-tuned neural representation of slight geometric structure (i.e., the Curb condition) and the impressive fine-grained sensitivity to slight 3D boundary cues that is manifested in behavioral reorientation from an early point in life (Lee & Spelke, 2008; 2011). Thus, I propose that there exists a chain between environmental boundaries, their geometric representation in the brain, and the navigational ability of reorientation.

In this thesis, I explore the three elements of this chain and the links between them. However, these connections may be difficult to discern in the healthy adult brain, in which

all facets of the navigation network are operating seamlessly as we move from place to place. A potential window to the function and representational structure of this network are cases in which certain facets have broken down. These instances of malfunction may reveal crucial aspects of spatial representation that are difficult to discern in the TD case, when all is operating fluidly. One such window is offered by the study of people with spatial disorders. Genetic disorders, which often present with spatial impairment, may provide especially unique insight that could be key to understanding whether sensitivity to boundaries constitutes a crucial piece of the navigation network that could be selectively damaged. As reviewed above, sensitivity to the geometric structure of the environment is a fundamental capacity for navigation by human children, adults, and animals. What is the cognitive and neural result when this sensitivity is diminished? Individuals with WS, who show impairments in a variety of navigation and spatial tasks, present a special case with the potential to shed light on this question.

The case of Williams syndrome

Lee and Spelke's (2008; 2011) findings demonstrate that vertical extensions of boundary structure are crucial input for the reorientation mechanism—even early in life, TD preschoolers possess finely-tuned sensitivity to this aspect of an environment's spatial layout. This sensitivity is so fine grained as to detect exceptionally subtle alterations in surfaces that signify the presence of a 3D boundary. However, research with members of a special population suggests that this finely tuned sensitivity may be impaired by genetic deficit. WS is a developmental disorder characterized by a well-defined set of approximately 25 genes missing on chromosome 7q11.23 (Morris, 2006a). The incidence estimate has been given as 1 in 7,500 (Strømme et al., 2002). WS is associated with mild to moderate mental retardation

or learning difficulties and is accompanied by a unique cognitive profile that includes severe impairment in a range of spatial functions (e.g., orientation discrimination (Palomares, Landau, & Egeth, 2009), object recognition (Landau, Hoffman, & Kurz, 2006) and visuo-manual action (Dilks, Hoffman, & Landau, 2008)), coupled with relative strengths in linguistic fluency (Musolino, Chunyo, & Landau, 2010; Zukowski, 2009) and verbal short-term memory (Mervis et al., 2000). Neurological problems include coordination difficulties (for example, walking down a staircase) (Meyer-Lindenburg et al., 2005), hyperreflexia, and hypersensitivity to sound (American Academy of Pediatrics, 2001; Chapman et al., 1996; Morris, 2006b). WS individuals have structural and functional abnormalities in the hippocampus and parietal areas (Meyer-Lindenburg et al., 2005; 2006), which are part of the network of brain regions that support navigation and may be key for representing scene boundaries.

Several studies indicate that people with WS have impairments in aspects of navigation. For example, Farran et al. (2012) found that WS participants made more errors and required more training trials than chronological age-matched controls to successfully learn a route through a virtual-reality environment. Nardini et al. (2008) found that even adults with WS have difficulty locating an object on an array that had been rotated, which changes the spatial relationships between all objects and available landmarks. However, both these studies indicate that some aspects of navigational ability are relatively preserved in WS. The WS participants in Farran's study *could* learn a route to criterion, even though this required more trials than controls. Nardini et al. (2008) found that participants were able to accurately locate objects in the array after they themselves had moved, showing that they could update their own position after movement. These findings indicate that both route

learning and updating of position following movement over short distances are both functional (to some degree) in the WS navigation system.

In contrast, people with WS appear to have particular difficulty when they are required to reestablish their heading direction following disorientation. Lakusta, Dessalegn, and Landau (2010) tested whether people with WS could use geometry to reorient themselves. They found that, of 19 people with WS (ages 9;9 – 27;7), only 5 used geometry. This suggests that members of the population are unable to use geometric information about layout to inform their search.

However, a recent replication suggests that this conclusion may be too strong (Ferrara & Landau, 2013). We modified the layout of the reorientation room to enhance the salience of the corners by removing the floor-length fabric panels that had been previously used by Lakusta et al. (2010). These panels effectively blurred the junctures of the walls, and may have served to obscure the overall geometry of the room (90° corners vs. 8 oblique corners, Figure 2.12). In this new environment, we found that of 16 WS children and adults (ages 5;8 – 32;8), 14 used geometry. This suggests that people with WS do show sensitivity to geometric information during reorientation, but may require especially salient presentation of the information for maximal use. The fact that modification of the room's boundary walls boosts geometric sensitivity within this spatially impaired population further illustrates the overall importance of boundaries as a cue for navigation, in cases of both atypical and typical development.

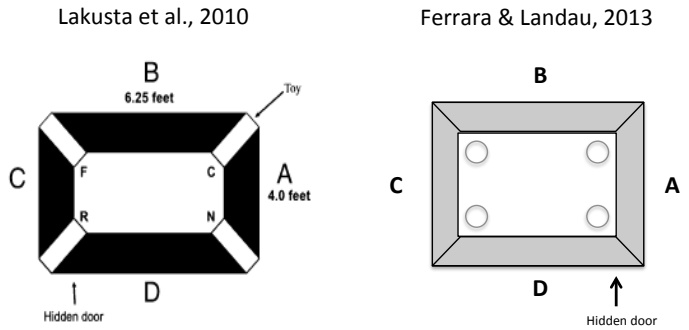

Figure 2.12: Floor plan of the room layouts used by Lakusta et al. (2010), left, and Ferrara & Landau (2013), right.

Neural bases of the WS spatial deficit

A growing body of research serves to show that the WS brain differs from those of TD individuals in a number of ways. At post mortem, reduced brain size has been observed (Jernigan & Bellugi, 1990), as well as shape changes in the corpus callosum (Tomaiuolo et al., 2002). Chiari malformations (structural defects in the cerebellum) are common (Mercuri et al., 1997; Pober & Filiano, 1995), in addition to abnormalities in the morphology of sulci and gyri (Gaser et al., 2006; Jackowski & Schultz, 2005).

Given their spatial impairments, one might except to find abnormalities in the WS brain in areas specifically known to be involved in spatial function. The hippocampus and parietal lobe are two such regions (as reviewed above). Studies using structural MRI have suggested that the reductions in size in the WS brain are localized in the parietal lobe (Eckert et al., 2005) and occipital grey matter (Reiss et al., 2000). Reductions in sulcal depth in the intraparietal sulcus have also been observed (Kippenhan et al., 2005; Van Essen, 2004), as well as abnormal white matter tracts connecting to this region (Marenco et al., 2007).

Researchers have begun to address the structural and functional role of the hippocampal formation in WS (Meyer-Lindenburg et al., 2005; 2006; Reiss et al., 2000). These studies have found grossly preserved volume of the hippocampus in high-functioning

individuals with WS, in comparison to controls matched for age, gender and IQ (Meyer-Lindenburg et al., 2005). However, a slight but consistently unusual morphology has been observed, even in high-functioning individuals with WS, with relative local volume reduction at the posterior apex (the tail-end of the hippocampus), and relative local volume expansion at the anterior base (extending from the midsection to the dorsal hippocampal head) (Meyer-Lindenburg et al., 2005). It is noteworthy that humans proficient in spatial navigation (i.e., London taxi drivers) show increased posterior but decreased anterior hippocampal volume (Maguire et al., 2000), which is the converse of the pattern observed in the case of WS. This suggests a relationship between hippocampal shape and navigation ability.

Further functional characterization of the hippocampal formation in people with WS has measured baseline neurofunctional status at rest (using oxygen/water positron emission tomography), which revealed that WS metabolic flow is severely reduced in comparison to controls (Meyer-Lindenburg et al., 2005). Reductions in resting blood flow have also been described in other disorders affecting hippocampal integrity and neuronal function, such as early Alzheimer's (Kogure et al., 2000), as well as the interictal period of temporal lobe epilepsy, just before seizure (Tae et al., 2005). Measures of cellular integrity and synaptic abundance using proton magnetic resonance spectroscopy have found reduced levels in the hippocampus of people with WS (Meyer-Lindenburg et al., 2005). These are indications that oxidative metabolism in the region is atypical, and it is known that long-term potentiation (thought to underlie learning/memory and potentially spatial learning/memory in particular (for review see Lynch (2004)) is highly dependent on this process (Meyer-Lindenburg et al., 2006).

Is the neurofunctional status of early visual processing also impaired in WS? A study that mapped the primary visual cortex (V1) suggests that its recruitment is grossly normal in this population. V1 size did not differ between WS individuals and chronological or mental age matched controls, and the average centers of gravity for the groups were similarly located near the fundus of the calcarine fissure, ~25mm away from the most posterior aspect of the occipital lobe (Olsen et al., 2009). In contrast, response to the spatial stimuli of houses has been found to shower lower activation than controls in dorsal and parietal regions (O'Hearn et al., 2011; Sarpal, 2008). Sarpal et al. (2008) found that adults with WS showed reliably lower activation of the right intraparietal sulcus (IPS) than TD adult controls, and O'Hearn et al. (2011) found WS individuals displayed less activation for houses than either chronological age or mental age controls (particularly in posterior and lateral regions). Both these studies found that the WS group showed no differences in activation during passive viewing of human faces, suggesting that reduced amounts of activation may be associated with spatial stimuli in particular.

Are reduced levels of activation also observable while individuals are engaged in spatial tasks? Meyer-Lindenburg and colleagues have observed neural activation as people with WS carried out a visuo-construction task. In the matching task (Figure 213.A), participants were shown two shapes and were asked whether they were the same or not. In the construction task (Figure 2.13.B), participants were shown two shapes and were asked to determine if they could be put together to make a square. No differences between WS participants and age-matched controls were found in ventral stream activation during either task, but significant hypoactivation in dorsal stream areas (parietal lobe) was found in the WS group, both when the matching task was compared to baseline (no visual stimulation),

and when the construction task was compared to the matching task (Meyer-Lindenberg et al., 2004).

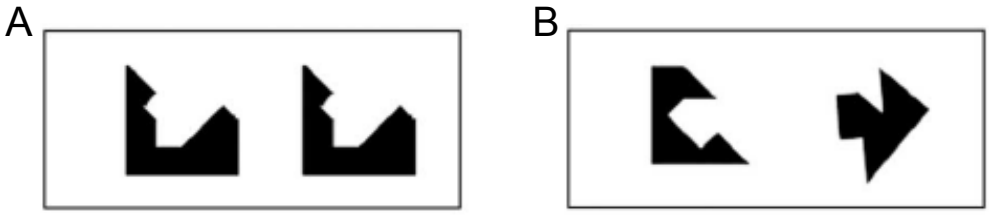

Figure 2.13: A) Matching task stimuli. B) Square completion stimuli (Meyer-Lindenberg et al., 2004).

Overall, there appears to be general weakness in dorsal stream function in WS, contrasted with relative strength in the ventral stream (Landau & Hoffman, 2012). This maps well to the known abnormalities in the parietal areas and hippocampus in people in WS. To date however, the only type of stimuli used to assess activation differences has been images of houses or 2D geometric figures. Given difficulties with geometric reorientation, another key WS impairment may lie in the representation of environmental boundaries in stimuli that convey the structural layout of scenes. Furthermore, might the neural processing of these types of stimuli be related to how people with WS use boundary cues in real-world navigation tasks? Investigation of this question within the WS population provides a unique opportunity to explore links between genes, behavior, and cognitive representation.

CHAPTER 3: TYPICAL AND ATYPICAL DEVELOPMENT OF REORIENTATION BY BOUNDARY CUES

In Experiment 1, the reorientation abilities of TD children and individuals with WS were tested using three types of arrays that differed in terms of boundary cue (a flat Mat, a Curb, and a full Wall, see Figure 3.1). Previous research has evaluated WS performance solely in arrays of full walls (too high for a person of average height to see over). The results of Lakusta et al. (2010) and Ferrara & Landau (2013) suggest that the WS reorientation mechanism may be intact, but fragile in that it appears to require the input of particularly salient geometric information to operate effectively. In contrast, four-year-olds require only the slightest suggestion of 3D vertical structure (Lee & Spelke, 2008; 2011). Will people with WS demonstrate this same sensitivity? Alternatively, will their performance illustrate a qualitatively different pattern from TD children? (i.e., will their deficits in spatial navigation result in insensitivity to the geometry of slight 3D boundaries?). I predict that while some individuals with WS will demonstrate geometric sensitivity in the full Wall condition, many will not do so in the Curb or Mat arrays. As previous research indicates that the WS reorientation mechanism is fragile, I hypothesize that the slight 3D vertical structure of the Curb will not be sufficient to trigger geometric sensitivity in this group.

Materials and methods

Participants

Eighteen TD four-year-olds (M = 4.55 years, Range = 4.0 – 5.05 years, SD = 0.38 years, 9 girls) and 18 TD six-year-olds (M = 6.51 years, Range = 6.0 – 7.16 years, SD = 0.33 years, 9 girls) participated in Experiment 1. At the end of the study, children chose a small toy to take home.

Fifteen individuals with WS (*M* = 22.37 years, Range = 12.38 – 36.13 years, *SD* = 4.96 years, 9 females) also participated in Experiment 1. All WS participants have the characteristic genetic deletion on the long arm of chromosome 7, as determined by FISH (fluorescent in situ hybridization) test. Participants were compensated financially.

As a control comparison group, fifteen TD people individually matched to the WS participants for gender and chronological age (CA controls) (*M* = 22.13 years, Range = 12.13 – 35.83 years, *SD* = 5.05 years, 9 females) participated in Experiment 1. Chronological age matches were made such that the WS and TD individuals had birthdays that were within 3 months of one another. Participants were compensated financially.

All participants had normal or corrected-to-normal vision. The study protocol was approved by the Homewood Institutional Review Board of Johns Hopkins University. Participants or their parents provided written informed consent for the study (in cases where participants were under the age of 18 or were not their own legal authorized representative, parents provided written informed consent and participants provided oral consent).

Standardized measures

To assess the overall cognitive profile of WS participants, the Kauffman Brief Intelligence test (K-BIT II; Kaufman & Kaufman, 2004), as well as specific subtests of the Differential Abilities Scale (DAS II; Elliott, 1990) were administered.[6] The K-BIT II is a standardized measure normed for TD individuals ages 4 – 90 years. It is comprised of three subtests: Verbal Knowledge, Riddles, and Matrices.

The Verbal Knowledge subtest measures receptive vocabulary and requires participants to respond by selecting one image among four that best illustrates the vocabulary

[6] In the interest of maintaining motivation and avoiding behavioral issues in the reorientation task, standardized measures were not administered to TD four- and six-year-olds.

word given by the examiner (e.g., "Point to *illuminate*"). The Riddles subtest measures verbal comprehension, reasoning, and vocabulary knowledge. The examiner asks a riddle, and the examinee either points to a picture that shows the answer to the riddle or says a single word that answers the riddle (e.g., "What is something that wags its tail and barks?"). The Verbal Knowledge and Riddles subtests are combined to obtain a Verbal score. For the Verbal score, average percentile rank for chronological age for WS participants was 17.33% (*SD* = 16.62%, Range = 1% – 68%).

The Matrices subtest is a nonverbal measure that is composed of several types of stimuli, both meaningful (people and objects), and abstract (designs and symbols). Success depends on the participant's ability to infer relationships among the stimuli and select a remaining item that follows the pattern of the relationships. The Matrices subtest provides a Nonverbal score. For the Nonverbal score, average percentile rank for chronological age for WS participants was 25.40% (*SD* = 16.90%, Range = 9% – 68%).

Combination of the K-BIT II Verbal and Nonverbal scores yields an overall composite IQ score. WS participants in the present study had an average IQ of 84 (*SD* = 9.69, Range = 67 – 109). This is higher than previous studies conducted by members of our lab (Lakusta et al. (2010), average IQ of 67.05; O'Hearn et al. (2011), average IQ of 67). However, in a study by Mervis et al. (1999), the WS individuals tested were found to have IQs that ranged from 40 (the lowest possible score) to 104. As Mervis et al. (2000) note, there is a great deal of variability in IQ scores among individuals with WS. In imaging studies conducted by Meyer-Lindenburg et al. (2004; 2005), 13 high-functioning individuals with WS (who has the classic 7q11.23 microdeletion) were specifically selected to participate because they had IQs within the normal range (these individuals had an average IQ score of

92.1). In the present study, 5 WS individuals fell within the "average" descriptive category for chronological age (as defined by the K-BIT II scoring criteria). Six individuals were within the "below average" descriptive category, and 1 was within the "lower extreme" range.

Four subtests of the DAS II were also administered: Pattern Construction, Digit Span (Forward and Backward), and Recall of Sequential Order. For these subtests, ability scores and age equivalents are reported because the DAS II is normed up to 18 years of age for TD individuals (thus determining the percentile for chronological age for participants over the age of 18 years is not possible). No WS participants performed at or above the age equivalent level of a TD 18-year-old on any of these subtests.

The Pattern Construction subtest of the DAS requires participants to copy the pattern of a model by assembling sets of blocks. It is a key diagnostic of the spatial deficit in WS (Mervis et al., 2000). The WS participants tested in the current study had an average ability score of 234.93 (*SD* = 44.20, Range = 104 – 276), and an average TD age equivalent of 8.43 years (*SD* = 2.24 years, Range = 3.33 – 11.25 years). This is consistent with the spatial deficit that has been observed for individuals with WS (Mervis et al., 2000).

The Digit Span (Forward) subtest requires participants to repeat ordered sequences of numbers that have been dictated to them by an experimenter. The Digit Span (Backward) subtest requires the participant to reverse the order of the numbers. On the Forward subset, WS participants had an average ability score of 152.33 (*SD* = 20.77, Range = 120 – 184), and an average TD age equivalent of 9.15 years (*SD* = 3.3 years, Range = 5.33 – 15.75 years). On the Backward subset, WS participants had an average ability score of 114.0 (*SD* = 25.33,

Range = 73 – 151), and an average TD age equivalent of 11.25 years (*SD* = 4.04 years, Range = 6.08 – 17.75 years).

In the Recall of Sequential Order subtest, the experimenter dictates a list of body part names, to which the participant responds by naming the body parts from the spatially highest to the lowest. For example, the correct response for "elbow, ankle, chin" is "chin, elbow, ankle." The WS participants tested in the current study had an average ability score of 95.93 (*SD* = 44.20; Range = 58 – 122), and an average TD age equivalent of 7.63 years (*SD* = 1.37 years; Range = 5.58 – 8.83 years).

Design

The experiment was conducted in a room with a uniform white circular hanging curtain that ran around the entire perimeter of the space. The floor was a solid gray rug. Ceiling lights were symmetrically spaced in a circle around the edge of the curtain. A hidden camera was located at the center of the ceiling. The room was protected from outside noise by four equally spaced white noise machines that were positioned outside the barrier of the curtain.

Each of the arrays for the different conditions were situated at the center of the chamber and measured 1.8 m × 1.2 m. Three separate rectangular arrays were used that varied in terms of vertical boundary cue: Mat, Curb, and Wall (Figure 3.1). For the Mat condition, a flat black mat was placed on the floor. For the Curb condition, connected wooden beams that stood 5 cm high were placed around the perimeter of the mat. For the Wall condition, the curb structure was removed and was replaced by panels covered in black felt that stood 2 m high. For all three conditions, circular black metal tins (3 cm high, 8 cm diameter) served as hiding spaces, which were placed at each of the four corners of the array.

Each participant completed the reorientation task in all three boundary cue conditions. The order of these conditions was counterbalanced within each participant group.

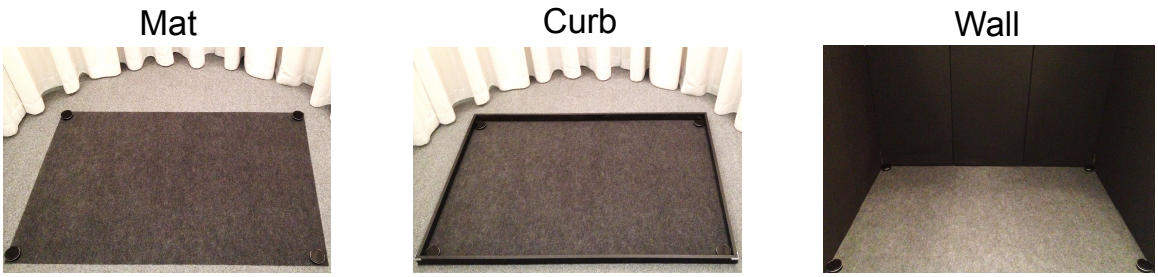

Figure 3.1: The three reorientation boundary conditions of Experiment 1: Mat, Curb, and Wall.

Procedure

Each participant was tested by the experimenter, while parents waited outside the room or in the lab. Following the original reorientation procedure (Hermer & Spelke, 1994; 1996), participants were brought into the rectangular array where they observed four stickers being hidden in a particular container located at one of the four corners. Participants were led to the center of the array and were blindfolded. The experimenter then guided participants as they spun around in place several times until disorientation was confirmed by the participant's inability to correctly point in the direction of the door to the room. The experimenter counted aloud while circling the participant in the opposite direction of their turns, in a rhythm that did not coincide with the rotations of the turns.

All participants started each trial facing the same wall (predetermined by the experimenter and counterbalanced across participant groups), but on each trial ended their rotation facing a different wall. Participants then removed their masks and were asked to pick the container that they thought held the sticker. One sticker at a time was removed on each of the four trials. If participants were incorrect in their first choice, they were encouraged to choose another location. If they were incorrect on their second choice, the experimenter led

them to the correct container. Thus, each trial ended with success and the reinforcement of a sticker. The location of the sticker and the order of the four facing directions were counterbalanced within each participant group.

Results

Analyses and preliminary findings

Searches were recorded from videotaped footage of the task. For all three conditions, all participants restricted their searches to the four corners of the array on 100% of the trials, showing that they detected the form of the array and remembered its relevance for the search task. To determine whether the disorientation procedure was effective and whether the arrays were devoid of inadvertent cues, searches at the correct corner were compared to searches at the geometrically equivalent opposite corner. These search rates did not differ in any of the conditions for any of the groups (for TD four-year-olds and six-year-olds all ts(17) < 1, ps > .05, and for WS participants and CA controls all ts(11) < 1, ps > .05. Specific means and standard errors for each corner of each array are provided in Figures 3.2, 3.4, 3.6, and 3.8 below). To test for gender differences in performance, the proportions of geometrically correct searches were compared for males and females within each group, within each condition. No gender differences were found (for TD four-year-olds and six-year-olds all ts(17) < 1, ps > .05, and for WS participants and CA controls, all ts(11) < 1, ps > .05). No order effects of condition were found for any group, all ts < 1, ps > .05. For all participant groups, performance in the first two trials did not differ significantly from performance in the last two trials, all ts < 1, ps > .05, indicating no improvement over trials.

The results below are reported separately for each boundary condition (Mat, Curb, Wall) for each participant group. Performance on the participant level is first evaluated by

comparing the number of participants who searched most often at the geometrically appropriate corners (*C*, *R*), to those who searched most often at the non-geometric corners (*N*, *F*), to those who searched the two corner types an equal number of times (i.e., two searches to each corner type). A chi-square goodness of fit test is used to determine whether these observed patterns differ significantly from what would be expected by chance alone.[7] These analyses are supplemented by testing the proportion of geometrically correct searches against chance (50%), using a two-tailed *t* test (following the analyses of Lee & Spelke, 2011). To correct for the multiple comparisons made within each group, the alpha level for significance was set to .0167 (Bonferroni correction for 3 comparisons performed within each group). Data from all four trials within each condition are included in the analyses below.

Typically developing four-year-olds

In these three symmetric rectangular arrays, participants who demonstrate reliance on geometry should evenly split their searches between the correct corner (*C*) and the one that is its rotational equivalent (*R*). The proportions of search to each of the four corners of the Mat, Curb, and Wall arrays are shown in Figure 3.2. Based upon the results of Lee & Spelke (2008; 2011), I hypothesized that the four-year-olds of the present study would demonstrate geometric sensitivity in the Curb and Wall conditions, but would search randomly in the Mat condition, which does not include vertical boundary structure.

In the Mat condition, 4 of the 18 TD four-year-olds searched most often at the geometrically appropriate corners (*C*, *R*), 7 participants showed the opposite pattern (i.e.,

[7] In much of the reorientation literature, performance is solely analyzed using parametric statistics that evaluate group proportions of search across the four corners (e.g., Hermer & Spelke, 1996; Learmonth et al., 2001; Lee & Spelke, 2008; Hermer-Vasquez et al., 2001). In the current study nonparametric statistics as included to consider performance on the participant level and to avoid violating the assumptions of parametric tests.

searched more often at the *N* and *F* corners), and 7 searched at the two corners types (geometric and non-geometric) an equal number of times. These data did not significantly differ from chance (50%): χ^2 (2, n = 18) of 1.0, p = .61. As shown in Figure 3.2, four-year-olds did not search at the *C* and *R* corners more than the *N* and *F* corners (46% geometric search, Cohen's d = –0.17, two-tailed $t(17)$ = –0.72, p = .48).

In the Curb condition, 11 of the four-year-olds searched most often at the geometrically appropriate corners, 2 participants showed the opposite pattern, and 5 searched at the two corners types an equal number of times. These data significantly differed from chance (50%): χ^2 (2, n = 12) of 7.0, p = .03. When reorienting in the Curb condition, four-year-olds restricted their search to the two geometrically correct corners (67% geometric search, Cohen's d = 0.61, two-tailed $t(17)$ = 2.61, p = .014). This stands as a replication of Lee & Spelke's (2008; 2011) findings.

In the Wall condition, 14 of the four-year-olds searched most often at the geometrically appropriate corners, 1 participant showed the opposite pattern, and 3 searched at the two corners types an equal number of times. These data significantly differed from chance (50%): χ^2 (2, n = 12) of 16.33, p < .0001. Considering their proportion of search, four-year-olds also restricted their searches to the geometrically appropriate corners in the Wall condition (83% geometric search, Cohen's d = 1.37, two-tailed $t(17)$ = 5.83, p < .001).

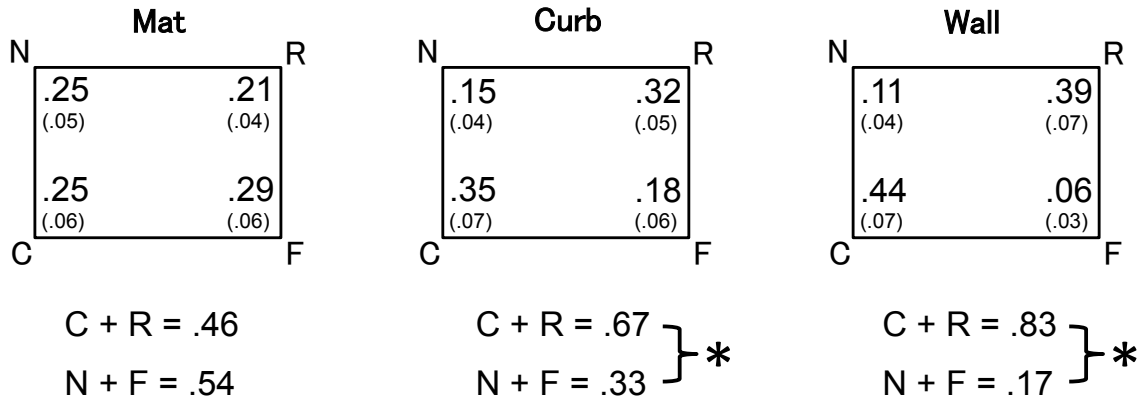

Figure 3.2: Proportions of search by TD four-year-olds (and one standard error of the mean) at the correct corner (*C*), the corner rotationally symmetric to the correct location (*R*), the nearby incorrect corner (*N*), and the farther incorrect corner (*F*). C + R indicates the total of geometrically correct searches, and N + F indicates the total of geometrically incorrect searches. Because hiding location varied across participants, all data have been rotated into alignment.

Considering geometric performance across all three boundary conditions, a repeated-measures ANOVA revealed a main effect of boundary, $F(2,34) = 9.88$, $p = .001$, $\eta_p^2 = .37$ (Figure 3.3). (All *p*-values reported in this thesis are Geisser-Greenhouse corrected for non-sphericity.) The Curb condition elicited more geometric searches than the Mat ($p < .05$ by Tukey's HSD test), and the Wall elicited more than the Curb ($p < .05$ by Tukey's HSD test). This indicates a stepwise pattern in the number of geometric searches that increases as the height of the boundary increases. This is a novel result not reported by Lee & Spelke (2008; 2011). I will later return to this finding in the Discussion.

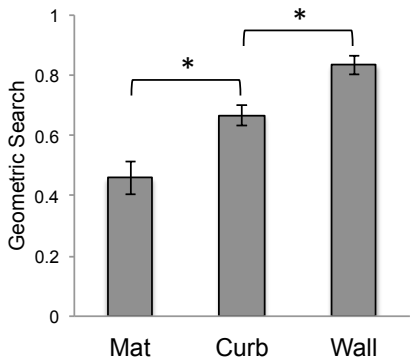

Figure 3.3: Proportion of geometric search (sum of searches to *C* and *R* corners) made by TD four-year-olds in the three boundary conditions. Error bars represent +/- standard error of the mean. Asterisks indicate significant difference between conditions, $p < .05$.

Typically developing six-year-olds

Like four-year-olds, I predicted that six-year-olds would reorient geometrically in the Curb and Wall arrays. I hypothesized that these older children may also reorient geometrically by the 2D Mat, as research has demonstrated that children of this age are able to use representational devices such as maps (Huttenlocher & Vasilyeva, 2003; Shusterman, Lee, & Spelke, 2008; Vasilyeva & Bowers, 2006). Figure 3.4 illustrates the proportions of search made by TD six-year-olds to each of the four corners in the different boundary conditions.

In the Mat, 9 of the 18 TD six-year-olds searched most often at the geometrically appropriate corners (*C*, *R*), 2 participants searched more often at the *N* and *F* corners, and 7 searched at the two corners types an equal number of times. These data did not significantly differ from chance (50%): χ^2 (2, $n = 18$) of 4.3, $p = .11$. However, *t* test analysis of the proportion of search to the geometrically appropriate corners indicated the six-year-olds were sensitive to the geometry of the Mat when reorienting themselves by this type of boundary, as a group searching more often at the *C* and *R* corners over the *N* and *F* corners (62% geometric search, Cohen's $d = 0.78$, two-tailed $t(17) = 2.03$, $p = .012$).

In the Curb, 13 of the six-year-olds searched most often at the geometrically appropriate corners, 2 participants showed the opposite pattern, and 3 searched at the two corners types an equal number of times. These data significantly differed from chance (50%): χ^2 (2, n = 18) of 12.33, p = .002. As a group, six-year-olds restricted their search to the two geometrically correct corners of the Curb array (72% geometric search, Cohen's d = 0.92, two-tailed $t(17) = 3.92$, p = .001).

In the Wall, 15 of the six-year-olds searched most often at the geometrically appropriate corners, 0 participants showed the opposite pattern, and 3 searched at the two corners types an equal number of times. These data significantly differed from chance (50%): χ^2 (2, n = 18) of 21.0, p < .0001. Six-year-olds searched more often at the geometrically appropriate corners when reorienting themselves by the Wall boundary (86% geometric search, Cohen's d = 1.84, two-tailed $t(17) = 7.82$, p < .001).

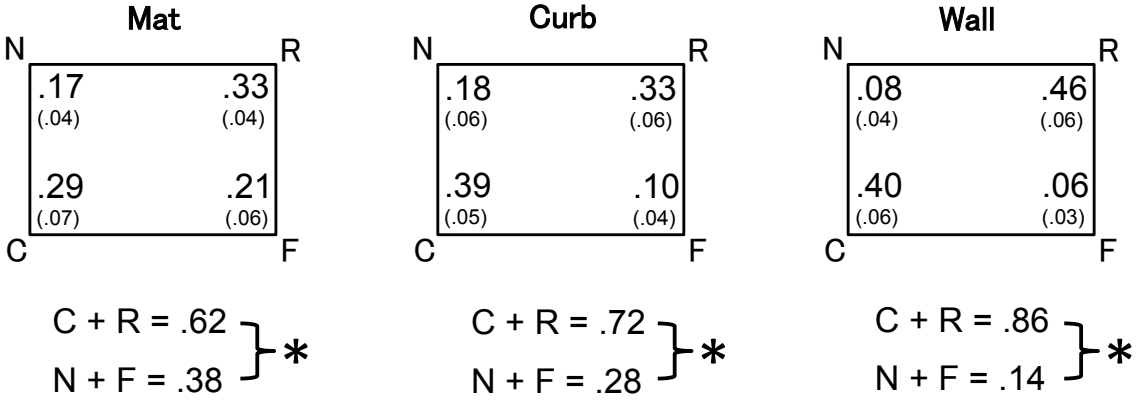

Figure 3.4: Proportions of search by TD six-year-olds (and one standard error of the mean) at the *C, R*, *N* and *F* corners.

As was found for four-year-olds, there was a main effect of boundary for the proportion of geometric searches made by six-year-olds across the three conditions, $F(2,34) = 7.71$, p = .003, η_p^2 = .312 (Figure 3.5). The Curb elicited more geometric searches than the Mat (p < .05 by Tukey's HSD test), and the Wall condition elicited more than the Curb (p <

.05 by Tukey's HSD test).

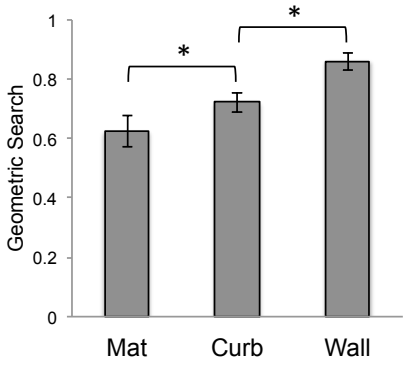

Figure 3.5: Proportion of geometric search (sum of searches to *C* and *R* corners) made by TD six-year-olds in the three boundary conditions. Error bars represent +/- standard error of the mean. Asterisks indicate significant difference between conditions, $p < .05$.

Participants with Williams syndrome

I predicted that WS individuals would reorient geometrically by the full Wall boundary (replicating the findings of Ferrara & Landau (2013)), but that geometric sensitivity may not be observed in the less salient boundary conditions of the Curb and the Mat. Figure 3.6 illustrates the proportions of search made by WS participants to each of the four corners in the Mat, Curb, and Wall arrays.

In the Mat, 5 of the 15 WS participants searched more often at the geometrically appropriate corners (*C*, *R*), 3 participants searched more often at the *N* and *F* corners, and 7 searched at the two corners types an equal number of times. These data did not significantly differ from chance (50%): χ^2 (2, $n = 15$) of 1.6, $p = .45$. Analysis of the proportion of geometrically correct searches showed that the WS participants chose amongst the four corners of the array at random (52% geometric search, Cohen's $d = 0.08$, two-tailed $t(11) = 0.29$, $p = .774$).

In the Curb, 3 of the WS participants searched most often at the geometrically appropriate corners, 7 participants showed the opposite pattern, and 5 searched at the two

corners types an equal number of times. These data did not significantly differ from chance (50%): χ^2 (2, n = 15) of 1.6, p = .45. As was observed for the Mat, WS participants did not restrict their searches to the geometrically appropriate corners when reorienting within the Curb array (45% geometric search, Cohen's d = –0.17, two-tailed $t(11)$ = –0.68, p = .51).

In the Wall, 12 of the WS participants searched most often at the geometrically appropriate corners, 0 participants showed the opposite pattern, and 3 searched at the two corners types an equal number of times. These data significantly differed from chance (50%): χ^2 (2, n = 15) of 15.6, p < .001. WS participants did demonstrate sensitivity to the geometry of the Wall boundary, searching more often at the correct and geometrically equivalent corners over the other two corner types (87% geometric search, Cohen's d = 1.76, two-tailed $t(11)$ = 6.81, p < .001).

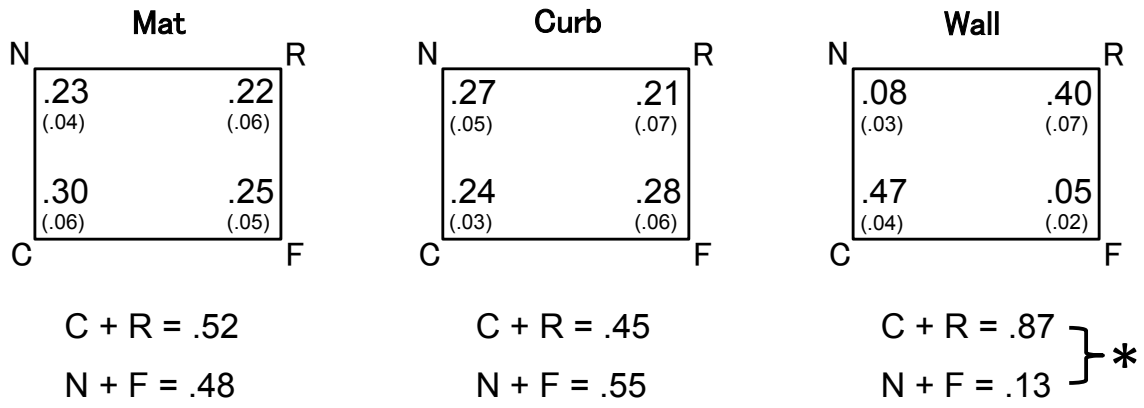

Figure 3.6: Proportions of search by WS participants (and one standard error of the mean) at the *C, R*, *N* and *F* corners.

As was found for TD children, there was a main effect of boundary for the proportion of geometric search made by WS participants across the three conditions, $F(2,28)$ = 14.05, p < .001, η_p^2 = .50 (Figure 3.7). However unlike TD children, the Curb condition did not elicit more geometric searches than the Mat for the WS group (p > .05 by Tukey's HSD test). It was still the case that the Wall elicited a greater proportion of geometric search than the Curb

($p < .05$ by Tukey's HSD test).

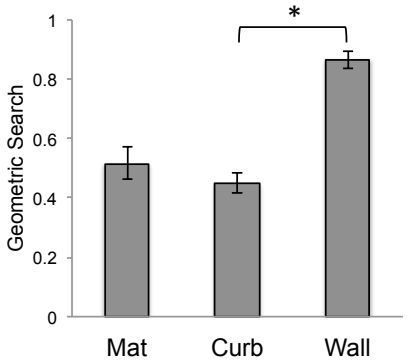

Figure 3.7: Proportion of geometric search (sum of searches to *C* and *R* corners) made by WS participants in the three boundary conditions. Error bars represent +/- standard error of the mean. Asterisk indicates significant difference between conditions, $p < .05$.

CA controls

It was predicted that CA controls would show geometric reorientation in the Curb and Wall arrays, and that also by adulthood, the ability to infer geometric structure from the abstract Mat boundary would be robustly demonstrated. Figure 3.8 illustrates the proportions of search made by CA controls to each of the four corners in the three boundary conditions.

In the Mat, 14 of the 15 CA controls searched most often at the geometrically appropriate corners (*C*, *R*), 0 participants showed the opposite pattern, and 1 searched at the two corners types an equal number of times. These data significantly differed from chance (50%): χ^2 (2, $n = 15$) of 24.4, $p < .001$. CA controls demonstrated sensitivity to the geometry of the Mat array, searching more often at the correct and geometrically equivalent corners over the other two corner types (88% geometric search, Cohen's $d = 2.40$, two-tailed $t(11) = 9.28$, $p < .001$).

In the Curb, all 15 of the CA controls searched most often at the geometrically appropriate corners. These data significantly differed from chance (50%): χ^2 (2, $n = 15$) of 30, $p < .001$. CA controls restricted their searches to the two geometrically correct corners in

the Curb array (90% geometric search, Cohen's $d = 3.16$, two-tailed $t(11) = 12.22$, $p < .001$).

In the Wall, all 15 of the CA controls searched most often at the geometrically appropriate corners. These data significantly differed from chance (50%): χ^2 (2, $n = 15$) of 30, $p < .001$). Again, CA controls restricted their searches to the geometric corners of the Wall array (97% geometric search, Cohen's $d = 5.31$, two-tailed $t(11) = 20.55$, $p < .001$).

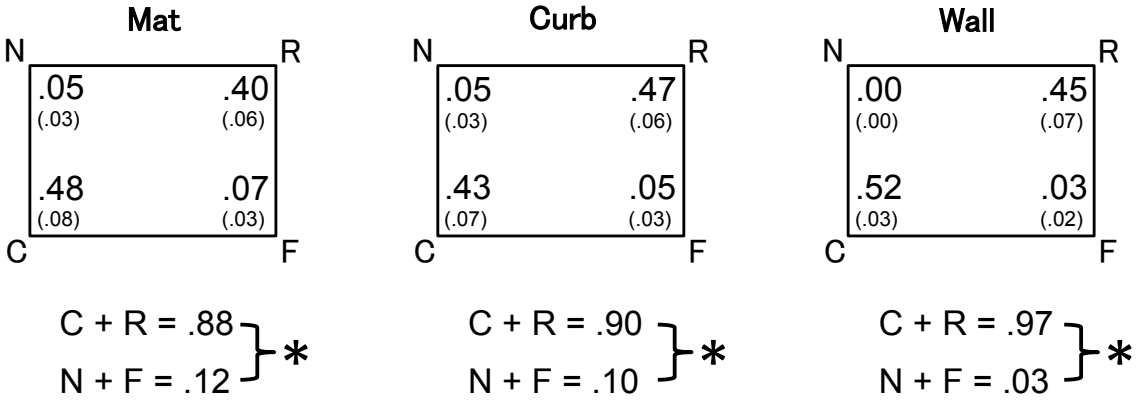

Figure 3.8: Proportions of search made by CA controls (and one standard error of the mean) at the *C, R*, *N* and *F* corners.

As CA controls performed near ceiling across all conditions (Figure 3.9), the main effect of boundary was not significant for the proportion of geometric search made within each condition, $F(2,28) = 2.04$, $p = .152$, $\eta_p^2 = .127$ (Figure 3.9).

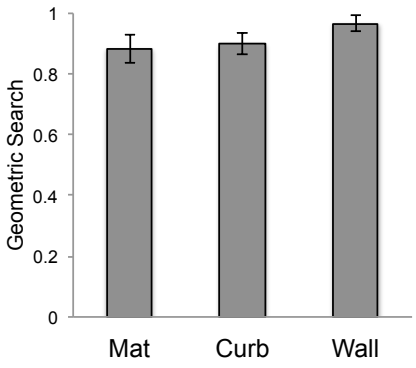

Figure 3.9: Proportion of geometric search (sum of searches to *C* and *R* corners) made by CA controls in the three boundary conditions. Error bars represent +/- standard error of the mean.

Discussion

In Experiment 1, TD four-year-olds, TD six-year-olds, individuals with WS, and CA controls were tested in three different boundary conditions of the reorientation task. For TD children, these results for four-year-olds replicate the findings of Lee & Spelke (2008; 2011). At this age, children demonstrate impressive sensitivity to the geometry of the minimal Curb structure, but this sensitivity does not extend to 2D boundaries such as the flat Mat. What might account for the failure of four-year-olds to reorient in 2D arrays? The underlying neural mechanisms required to support this process may not yet be fully developed. The medial temporal lobe undergoes protracted structural development well into middle childhood. Specifically, the hippocampus continues to develop until age 8 or 9 (Alvarado & Bachevalier, 2000; Gogtay et al., 2006; Seress, 2001; Utsunomiya, Takano, Okazaki, & Mitsudome, 1999). Further longitudinal research has documented that, although the overall volume of the hippocampus does not change from age 4 to 25, the anterior hippocampus decreases in volume between ages 4 and 25, whereas the posterior hippocampus increases during this period (Gogtay et al., 2006). An fMRI study of children ages 7 – 16 years has also documented development of the PPA: the size of the area recruited during spatial encoding increases with age, and significantly predicts subsequent recognition memory for scenes (Golarai et al., 2007). Given this protracted pattern of development across the navigation network, one might predict that geometric reorientation in 2D arrays may only be possible in late childhood.

However, the performance of six-year-olds indicates that the reorientation mechanism has evolved to also function efficiently over the input of 2D surfaces in childhood, while medial temporal structures are still undergoing significant developmental change. Six-year-

olds did demonstrate sensitivity to the geometry of the flat Mat array, and restricted their searches accordingly. As 2D information can sometimes provide important information about spatial location (featural variations in color can function as useful landmarks, for example), it follows that relatively immature navigators (i.e., six-year-olds) should be able to infer the geometry conveyed by 2D arrays. This coincides with the developmental time point at which children are able to use the featural cue of one colored wall in the reorientation task (in a 4 × 6 ft chamber, Hermer-Vasquez, Moffet, & Munkholm (2001)). Further evidence demonstrating children's ability to infer 3D spatial relationships from 2D information comes from studies of map reading (Huttenlocher & Vasilyeva, 2003; Shusterman, Lee, & Spelke, 2008; Vasilyeva & Bowers, 2006). Furthermore, a recent study has found a connection between map reading and navigation ability, in that use of distance and directional relations in reorientation predicts children's use of a symbolic map (Dillon, Huang, & Spelke, 2013). These results support the present finding that young children have the ability to form abstract representations of geometry that can be used when reorienting in 2D arrays. By the time children are six years of age, they are sensitive to more abstract indications of geometric structure, and use this information to inform their navigation. Thus, it appears that what "counts" as a boundary changes across the course of development. As we grow and develop, types of information other than 3D vertical structure (changes in texture, color, etc.) become sufficient to signify meaningful boundaries in the environment.

Another finding from Experiment 1 is that for four- and six-year-olds, the proportions of geometric search incrementally increased as the height of the boundary increased. That is, the number of geometric searches made in the Wall condition is significantly higher than those made in the Curb, which in turn is higher than those made in the Mat. (In CA controls

we see a ceiling effect, where the stepwise pattern has disappeared, and the Mat is used just as effectively as the Wall.) Even though the Curb and Wall both categorically qualify as "geometric" search patterns for four- and six-year-olds, the difference in the number of searches made to the C and R corners indicates that prominent walls are the most effective boundary for reducing error. Although this trend has been hinted at in previous studies (Lee & Spelke, 2008), analysis of the number of geometric searches is a novel approach in the reorientation literature.

The gradient pattern of geometric search was not observed for the WS group. In contrast to TD children and CA controls, WS participants did not demonstrate sensitivity to the geometry of the Curb condition in reorientation. This documents impairment to the reorientation mechanism in this genetic disorder. Notably however, both this study and Ferrara & Landau (2013) found that WS individuals were able to reorient geometrically when provided with the boundary of full walls. In light of these findings, I propose that the WS geometric impairment is characterized by a reduced sensitivity to geometric structure, requiring especially salient presentation of geometry if it is to be used to accomplish reorientation. That is, reorientation ability is not entirely erased in this disorder, but rather input to the reorientation mechanism must meet a much higher threshold (i.e., full walls, not minimal curb structure) in order to effectively inform reorientation. As described in Ferrara & Landau (under review), I speculate that the WS spatial deficit may be related to reduced sensitivity to metric variables more generally. This is consistent with other findings about the WS profile, which include reduced sensitivity to estimated numerosity (Libertus, Feigneson, Halberda, & Landau, 2014) and orientation in manual posting through a slot (Dilks et al., 2008). Collectively, these findings suggest that the deficits shown by WS individuals may

best be characterized as noisy structure, rather than qualitative differences in structure (Dilks et al., 2008).

Relationship to IQ

I asked whether the geometric performance of WS individuals is related to their scores on standardized IQ measures; the K-BIT, which yields an overall IQ composite score, the Pattern construction subtest of the DAS (a strong diagnostic of the WS spatial deficit, Mervis et al., 2000), or measures of working memory and recall (Digits Forward and Backward, and Recall of Sequential Order DAS subtests). Table 3.1 below illustrates the results of partial correlations (controlling for age) and the number of geometric searches made in the Mat, Curb, and Wall reorientation conditions. (None of these partial correlations were found to be significant for CA controls, all *p*s > .34).

Table 3.1: Partial correlations (*r* values) between WS scores on standardized IQ measures and proportions of geometric search made in the Mat, Curb, and Wall reorientation conditions. Significant correlations are marked with an asterisk, $p < .05$.

	K-BIT Composite	Pattern Construction	Digits (Forward)	Digits (Backward)	Sequential Order
Mat	.70 *	.42	.36	.65 *	.61 *
Curb	.31	–.07	.32	.43	.34
Wall	.25	.32	–.10	–.01	.25

These analyses revealed three significant correlations of interest between geometric performance in the Mat condition and the K-BIT IQ composite score, $r(9) = .70$, $p = .024$, score on the Digits (Forward) subtest, $r(9) = .65$, $p = .044$, and score on the Recall of Sequential Order subtest, $r(9) = .61$, $p = .05$ (Figure 3.10). The fact that a positive relationship is found for three different measures provides a robust indicator that some aspect of IQ does play a role in the ability of WS participants to reorient geometrically in

specifically the Mat condition. The Digit and Sequential Order measures in particular tap working memory.

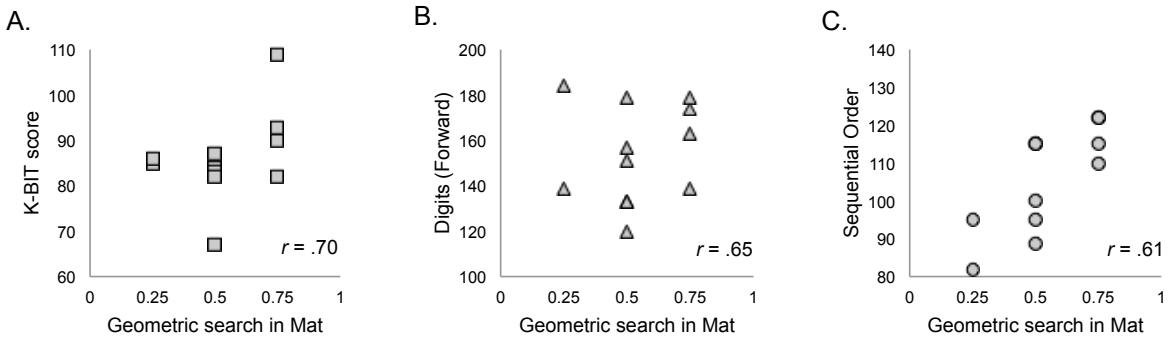

Figure 3.10: Correlation between WS performance on A) K-BIT composite IQ score, B) Digits (Forward) memory measure, and B) Recall of Sequential Order memory measure, and the proportion of geometric searches made by WS participants in the Mat array of the reorientation experiment (four trials).

How might these abilities be selectively involved in reorientation by a 2D boundary? In a virtual reality reorientation experiment, Sutton et al. (2012) compared neural activity for reorientation within a flat rectangular floor array to reorientation within a room with full walls. The floor trials did not result in significantly greater brain activation across any region in comparison to the walls. However, the authors speculate that the "lower salience of the floor cue may have resulted in adults compensating with other strategies to remember the correct corner. For instance, they might have encoded the relative lengths of the floor on each side of a target corner (e.g., long wall on the left, short wall on the right), similar to the walls condition, but then relied more heavily on verbal coding to remember the floor lengths in the absence of highly salient visual stimuli (such as walls)." I hypothesize that successful reorientation by 2D boundaries involves strategic inferences of geometry, as described by Sutton et al. (2012). Geometric reorientation in the Mat condition was accomplished by WS participants who had higher scores on general IQ and working memory measures, which contributed to successful implementation of these strategies. This is consistent with our

previous research of WS reorientation performance in arrays that include a landmark (Ferrara & Landau, under review). We found that successful use of the landmark cue was accompanied by a strategic, sequential step-by-step process that was used most effectively by adults with WS.

Although Lee and Spelke (2008; 2011) did not investigate the role of IQ in their studies of TD children, their results suggest that 3D continuous boundaries are the primary form of input to the reorientation mechanism. Reorientation by 2D boundaries, then, necessarily involves a different mechanism and/or encoding process that is not present early in life. The current findings demonstrate that children reorient by 2D boundaries by the time they are six years old. A multitude of behavioral and neural changes occur in the intervening years between age four and age six, but one contributing factor may be the ability to employ strategies and to maintain sequential strategic steps in memory. Unfortunately IQ was not tested in the current study for TD children, but the WS findings suggest that IQ is selectively related to geometric performance in one condition (the Mat), but not others (the Curb or Wall).

CHAPTER 4: TYPICAL AND ATYPICAL NEURAL SENSITIVITY TO BOUNDARY CUES

Experiment 1 documents the behavioral performance of TD children and people with WS when reorienting within arrays defined by different boundaries. It was found that, in contrast to TD children and CA controls, individuals with WS did not demonstrate sensitivity to the geometry of the Curb array. Would evidence of this lack of sensitivity also be found at the neural level? Experiment 2 tests the hypothesis that abnormalities observed at the behavioral level for the WS population are correlated with atypical patterns of neural encoding. Specifically, I hypothesize that the PPA of individuals with WS will not show sensitivity to the presence of a minimal amount of vertical boundary structure within a scene. I predict that data collected from the group of TD individuals matched to the WS participants for age and gender will replicate the results of Ferrara & Park (2014), in that the PPA in the healthy adult brain will show specific sensitivity to the slight Curb boundary in visually presented scenes.

Materials and methods

Participants

Twelve individuals with WS (M = 22.11 years, Range = 15.38 – 33.74 years, SD = 4.80 years, 7 females, 1 left-handed) participated in Experiment 2. TD CA controls were matched to WS participants for chronological age and gender (M = 22.03 years, Range = 15.13 – 34.0 years, SD = 4.87 years, 7 females, none left-handed). All WS individuals and CA controls tested in Experiment 2 also participated in Experiment 1.

Participants received financial compensation. The study protocol was approved by the Institutional Review Board of the Johns Hopkins University School of Medicine. Participants

or their parents provided written informed consent for the study (in cases where participants were under the age of 18 or were not their own legal authorized representative, parents provided written informed consent and participants provided oral consent).

Visual stimuli

Scene stimuli were used that closely approximate the physical arrays used in Experiment 1 (Mat, Curb, Wall). Full-color artificial images were created to manipulate the type of boundary present within a scene. There were three different boundary conditions: Mat, Curb, and Wall (Figure 4.1). Twenty-four different textures were used to introduce variability within the images. The complete stimulus set included 72 different images (3 boundary conditions × 24 textures). Images were 800 × 600 pixel resolution (4.5° × 4.5° visual angle), and were presented in the scanner using an Epson PowerLite 7350 projector (type: XGA, brightness: 1600 ANSI Lumens).

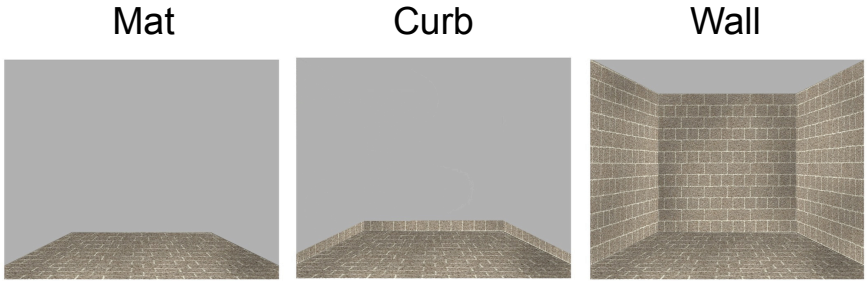

Figure 4.1: Illustration of the three conditions of Experiment 2, shown for one of the 24 textures used.

Experimental design

Ten images from one of the three conditions were presented in blocks of 12 s each. Three blocks per condition were acquired within a run (188 s, 94 TRs), and the order of blocks was randomized within each run. An 8 s fixation period followed each block. Each image was displayed for 1 s within a block, followed by a 200 ms blank. Participants

performed a one-back repetition detection task in which they pressed a button whenever there was an immediate repeat of an image (Figure 4.2). All participants completed 8 runs of the experiment, for a total of 24 blocks per condition.

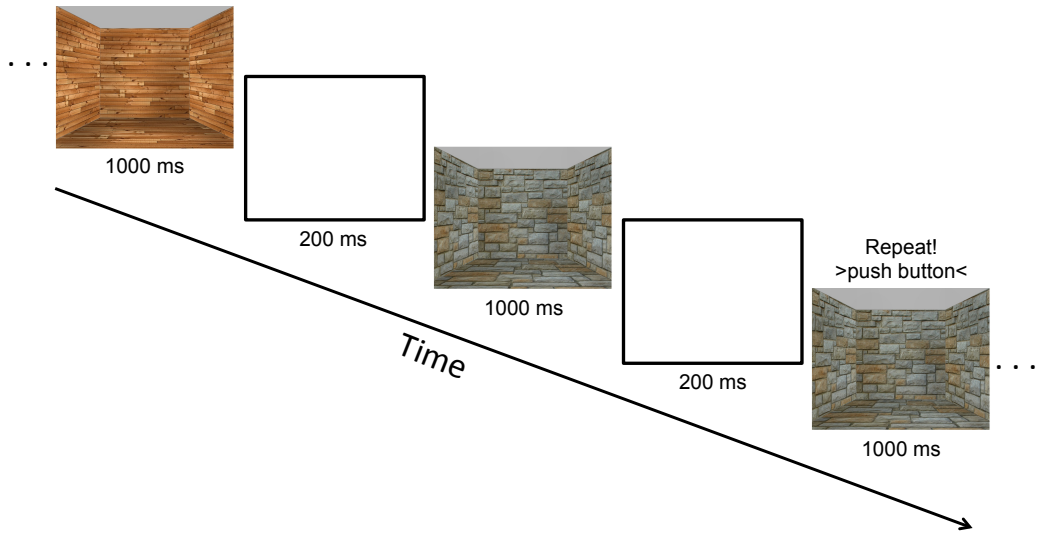

Figure 4.2: Illustration of the presentation of images within a block, including the one-back repetition detection task.

Simulation

To familiarize WS participants to the scanner environment, a simulated fMRI scanner was used. This method has proven successful in acclimating child participants (Rosenberg et al., 1997). Participants laid on a platform in the "pretend magnet" and practiced keeping still. The noise of the operating scanner was played through speakers so that participants would be accustomed to it in the scanning environment. A mirror and visual display similar to the real scanner was also used to present images, and participants practiced the one-back repetition task and received feedback if necessary. (None of the stimuli used in these practice trials were repeated during the actual experiment.) Practice of behavioral tasks prior to the actual scan has also proven beneficial for scanning child participants, who, without practice, tend to use visual checking methods (i.e., looking down at the button box and their hand) to insure that they are responding correctly (Thomas & Casey, 1999).

fMRI data acquisition

Imaging data were acquired with a 3-Tesla Phillips fMRI scanner with a 32-channel phased-array head coil at the F. M. Kirby Research Center at Johns Hopkins University. Participants were instructed to relax, stay still, and watch the pictures. Padding was placed around each participant's head to stabilize head position and reduce motion-related artifacts during scanning. Earplugs were worn by all participants, and 7 of the WS participants also chose to wear over-ear head phones to further reduce scanner noise. For all WS participants, an experimenter or family member remained present in the scanning room for the duration of the experiment. Structural T1-weighted images were acquired using a magnetization-prepared rapid-acquisition gradient echo (MPRAGE) with 1 × 1 × 1 mm voxels. Functional images were acquired with a gradient echo-planar T2* sequence (2.5 × 2.5 × 2.5 mm voxels; TR 2 s; TE 30 ms; flip angle = 70°), 36 axial 2.5 mm slices [.5 mm gap]; acquired parallel to the anterior commissure-posterior commissure line).

fMRI data analysis

Functional data were preprocessed using Brain Voyager QX software (Brain Innovation, Maastricht, Netherlands). Preprocessing included slice scan-time correction, linear trend removal, and three-dimensional motion correction. For univariate and multivariate pattern analysis, no additional spatial or temporal smoothing was performed and data were analyzed in each individual's ACPC space. For retinotopic analysis, the cortical surface of each subject was reconstructed from the high-resolution T1-weighted anatomical scan, acquired with a 3D MPRAGE protocol. These 3D brains were inflated using the BV surface module, and the obtained retinotopic functional maps were superimposed on the surface-rendered cortex.

Definition of regions of interest

Regions of interest (ROIs, Figure 4.3) were defined for each participant in individual ACPC space using a localizer. A localizer run presented blocks of images of scenes, faces (half female, half male), real-world objects, and scrambled objects. Scrambled object images were created by dividing intact object images into a 16 × 16 square grid and then scrambling positions of the resulting squares based on eccentricity (Kourtzi & Kanwisher, 2001). There were four blocks per each image condition (scenes, faces, objects, and scrambled objects), presented for 16 s with 10 s rest periods in between. Within each block, each image was presented for 600 ms with 200 ms fixation, and there were 20 images per block. Participants also performed a one-back repetition detection task during these blocks. The retinotopic localizer presented vertical and horizontal visual field meridians to delineate the borders of retinotopic areas (Spiridon & Kanwisher, 2002). Triangular wedges of black and white checkerboards were presented either vertically (upper or lower vertical meridians) or horizontally (left or right horizontal meridians) in 12 s blocks, alternating with 12 s blanks. During these blocks participants were instructed to fixate on a small central fixation dot.

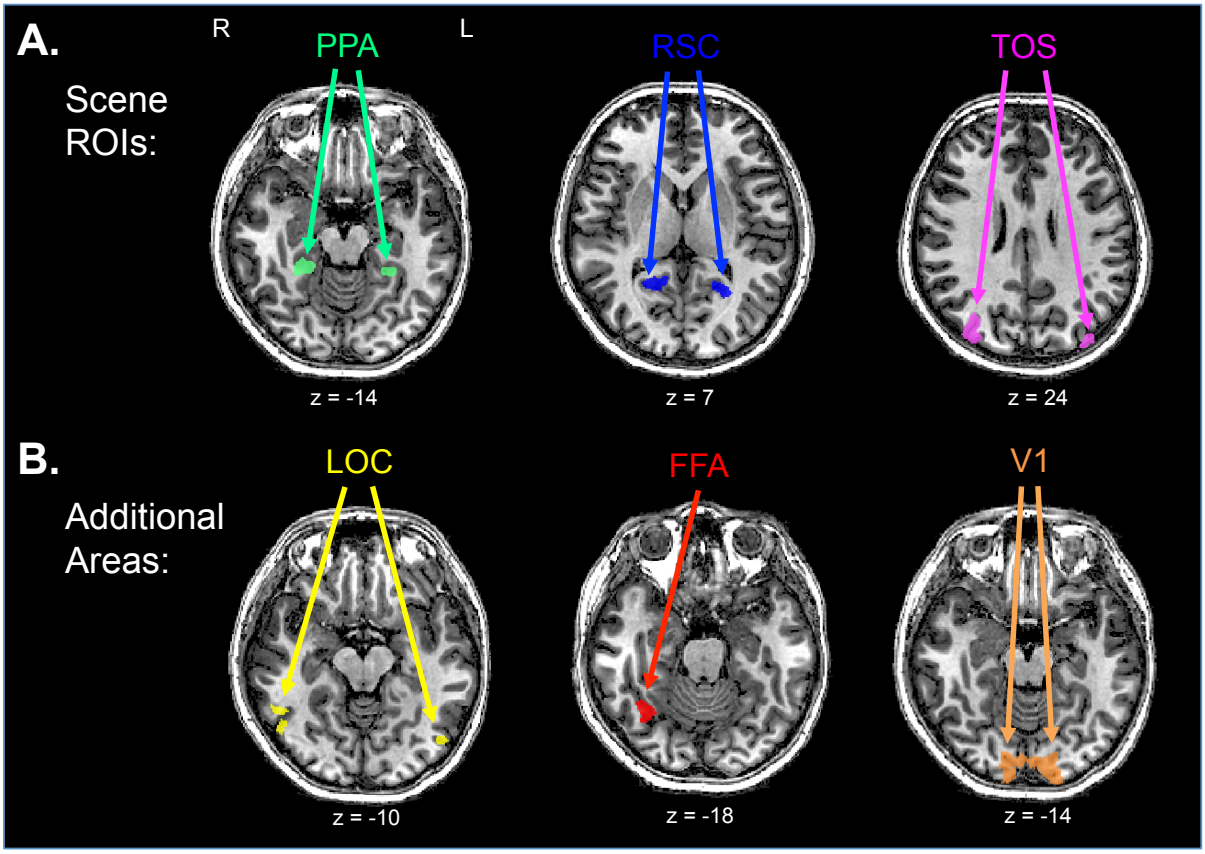

Figure 4.3: Regions of interest shown on a representative participant's brain. 4.3.A shows specific scene-selective areas of interest, and 4.3.B shows additional ROIs that were analyzed.

The entire cluster of voxels that passed the threshold of an ROI localizer ($p < .0001$, cluster threshold of 4 voxels) was used for all functionally defined ROIs. The left (L) and right (R) PPA were defined separately for individual participants by contrasting brain activity of scene blocks – object blocks and identifying clusters between the posterior parahippocampal gyrus and anterior lingual gyrus. This contrast also defined L and R RSC near the posterior cingulate cortex, and L and R TOS near the transverse occipital sulcus. The size and location of each ROI are summarized in Table 4.1, as well as the number of participants for whom each ROI was defined. When an ROI was not defined for a given participant, this was due to either a lack of activity for the localizer contrast in the anatomical

location of interest, or a cluster of active voxels that did not pass the cluster threshold of 4 voxels. It is perhaps notable that RSC was defined in 9 out of the 12 WS participants, but all 12 of the CA controls. However, even in studies of TD adults it is not uncommon that RSC is not defined in all participants (e.g., Dilks et al., 2011; Harel, Kravitz, & Baker, 2013; Park & Chun, 2009). A larger sample of WS individuals would be needed in order to make conclusions about the potential reduced presence of RSC in the population as a whole.

L and R lateral occipital complex (LOC, Grill-Spector et al., 2001; Kourtzi & Kanwisher, 2001; Malach et al., 1995) were defined by contrasting brain activity of objects – scrambled objects in the lateral occipital lobe. FFA was defined by contrasting brain activity of faces – scenes in in the right fusiform gyrus of the occipitotemporal cortex. FFA was only defined in the right hemisphere, reflecting the typical right-sided lateralization of this region (Kanwisher et al., 1997).[8] The retinotopic borders of L and R V1 were defined by a contrast between vertical and horizontal meridians. (Average peak Talaraich coordinates are not provided for V1 in Table 4.1 because this is not possible when defining ROIs using the inflation method described above.)

[8] In recognition of the possibility that individuals with WS may not show the same lateralization as has been observed in the TD population, it was verified that although FFA in the right hemisphere was identified for all 12 CA controls and all 12 WS participants, it was not likewise identified in the left hemisphere for all participants (9/12 CA controls and 10/12 WS participants). Although conclusions about the lateralization of FFA in the WS population as a whole cannot be drawn from this small sample, based upon these data I opted to analyze solely right FFA at the suggestion that it may be right-lateralized to some degree in WS and to be consistent with the literature.

Table 4.1: Number of participants that showed each ROI by hemisphere, as well as the average peak Talaraich coordinates for each ROI by hemisphere.

		Number of participants		Average peak Talairach coordinates (*x*, *y*, *z*)	
	ROI	LH	RH	LH	RH
WS	PPA	12	12	-23, -48, -8	20, -44, -10
	RSC	9	9	-20, -60, 8	18, -53, 6
	TOS	10	9	-34, -83, 21	35, -77, 23
	LOC	10	10	-41, -80, -2	40, -74, 1
	FFA		12		36, -49, -15
	V1	10	10		
CA	PPA	12	12	-27, -48, -8	23, -47, -9
	RSC	12	12	-20, -60, 11	17, -57, 12
	TOS	11	11	-35, -80, 16	35, -77, 20
	LOC	12	12	-43, -74, -5	43, -71, -2
	FFA		12		31, -54, -19
	V1	11	11		

LH, left hemisphere; RH, right hemisphere

Spherical ROIs

An additional method of defining all ROIs was employed such that the number of voxels was kept constant across both the WS and CA groups. Following the method of Park & Chun (2009), a maximally scene-selective voxel was localized for each hemisphere within the functionally and anatomically defined features for the particular ROI. These coordinates were then entered into the Brain Voyager QX Plug-in "Talairach coordinate to spherical VOI" to create spherical ROIs around the maximum voxel (4 mm radius). All univariate analyses detailed below were also performed separately using these spherical ROIs. No differences for WS participants or CA controls were found between results based upon analyses of either the entire cluster of voxels that passed the threshold of $p < .0001$ or those of the spherically-defined ROIs.

Univariate analysis

A general linear model (GLM) was computed to obtain estimates of the overall average activity in the ROIs. The GLM was computed on the time courses obtained for each ROI to extract beta values that provide an estimated effect size of the univariate response for each boundary condition. Motion parameters were included in the GLM to potentially reduce noise (Johnstone et al., 2006). Each block of conditions was separately estimated by the hemodynamic response function, and entered as predictors in the GLM.

Divided ROI analysis for anterior and posterior PPA

Previous research suggests that the PPA is comprised of functionally distinct sub-regions along the anterior/posterior axis (Bar & Aminoff 2003; Epstein 2008; Baldassano et al., 2013; Fairhall et al., 2013). To further investigate sensitivity within this ROI, I conducted an additional analysis in which the PPA of each participant was divided into four separate ROIs: PPA 1, PPA 2, PPA 3, and PPA 4 (see Figure 4.10). This was accomplished by a split-half analysis within each individual's functionally localized PPA (dividing it into two halves, according to the total number of voxels in length along the *y*-axis). The split-half analysis was then performed again on each half, resulting in 4 portions. Thus, PPA 1 and 2 are described as anterior, and PPA 3 and 4 are described as posterior.

Whole-brain analysis

Whole-brain analyses were conducted to compare sensitivity to the different boundary conditions in brain areas potentially beyond the specified ROIs. It is possible that the WS brain may show areas that differ from CA controls in this respect. To conduct this group analysis, each participant's data were normalized to a common brain template (the MNI EPI template, using methods based on the NeuroElf toolbox, Jochen Weber,

http://neuroelf.net/).[9]

Contrasts specified a priori were: (1) Mat < Curb and (2) Curb < Wall. These within-subject contrasts were combined into group random-effects analyses with a threshold of $p < 0.001$ (corrected for serial correlations; cluster threshold = 4 voxels). This threshold follows prior convention for exploratory whole-brain analyses (Epstein et al., 2007a; Johnson et al., 2007; Yi et al., 2008). Fixed-effects whole brain analyses were performed with a threshold of $p < 0.0001$ (corrected for serial correlations, cluster threshold = 4 voxels) in individual participants to confirm whether the regions that show up in the group-level random-effects analyses replicate at the individual level.

Multivoxel pattern analysis

Patterns of activity were extracted across the voxels of an ROI for each block of the three boundary conditions. The MRI signal intensity from each voxel within an ROI across all time points was transformed into z-scores by run, so that the mean activity was set to 0 and the SD was set to 1. This helps mitigate overall differences in fMRI signal across different ROIs, as well as across runs and sessions (Kamitani & Tong, 2005). The activity level for each block of each individual voxel was labeled with its respective condition, which spanned 12 s (6 TR), with a 4 s (2 TR) offset to account for the hemodynamic delay of the blood oxygenation level-dependent (BOLD) response. These time points were averaged to generate a pattern across voxels within an ROI for each stimulus block.

For each ROI of each participant, a separate linear support vector machine (SVM) classifier was used (LIBSVM, http://sourceforge.net/projects/svm/). A leave-one-out cross validation method was employed, in which one of the blocks was left out from the training

[9] Note however that all other analyses reported in this thesis are conducted on data in native ACPC space.

sample. This cross-validation method was repeated so that each block of the dataset played a role in training and testing. Twenty-four cross validation iterations were run (24 blocks per condition, left out of the training set for testing one time each).

To equate the number of voxels selected for analysis across the WS and CA groups, a randomly sampled set number of voxels (e.g., 500) was selected from each ROI of each participant. Different set numbers of voxels were tested for the ROIs (20, 100, 500, and 1,000 voxels). This process was repeated 50 times for each set number of voxels within each ROI in each participant. Classification accuracy plateaued at 500 voxels and was equal to classification performance when all the voxels within the ROIs were included (replicating Park et al., 2011). The analyses detailed below are performed on the classifier results when 500 voxels were selected for both the CA and WS groups.

Results

Whole-brain volume

Using the BrainVoyager QX segmentation tool, the skull and head tissue was removed from the brain of each participant. The entire remaining volume was then selected to obtain a count of the total number of voxels in the brain. This did not differ between CA controls (M = 1236230.75 voxels, SD = 93992.11 voxels) and WS participants (M = 1178360.25 voxels, SD = 76756.05 voxels), Cohen's d = 0.68, two-tailed $t(22) = 1.65$, p = .113.

Size of ROIs

For all analyses reported below, the individual WS and CA pairs were taken into consideration, such that if an ROI was not defined for a particular participant, the data from their corresponding match was not included in the analysis of interest.

Two-way mixed analyses of variance (ANOVA) were computed to compare the number of voxels for each right and left hemisphere ROI between the WS participants and CA controls (Figure 4.4). For the PPA, the main effect of the within-subject factor Hemisphere (RH, LH) was not significant, $F(1,22) = 2.01$, $p = .17$, $\eta_p^2 = .08$. However, the main effect of the between-subjects factor Group (WS, CA) was marginally significant, $F(1,22) = 3.64$, $p = .07$, $\eta_p^2 = .14$. The Group by Hemisphere interaction was not significant, $F(1,22) = 0.15$, $p = .705$, $\eta_p^2 = .007$.

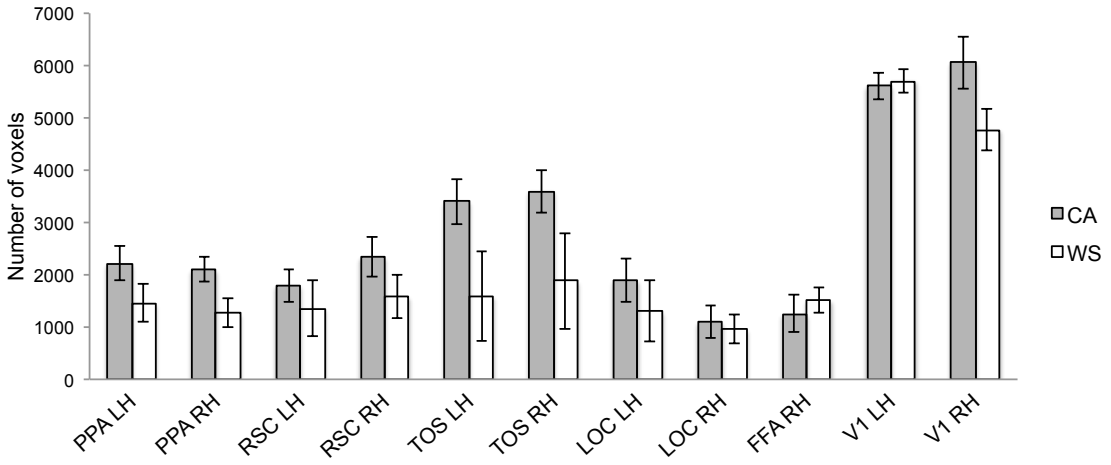

Figure 4.4: Average number of voxels for each of the ROIs (after mapping into the structural 1 x 1 x 1 voxel space) for WS participants and CA controls. (LH = left hemisphere; RH = right hemisphere.) Error bars represent +/- standard error of the mean.

For RSC, The main effect of Hemisphere was not significant, $F(1,16) = 0.03$, $p = .874$, $\eta_p^2 = .002$, nor was the main effect of Group, $F(1,16) = 2.73$, $p = .118$, $\eta_p^2 = .146$. The Group by Hemisphere interaction was also not significant, $F(1,16) = 0.89$, $p = .36$, $\eta_p^2 = .053$. For TOS, the main effect of Hemisphere was not significant, $F(1,16) = 2.01$, $p = .17$, $\eta_p^2 = .084$, The main effect of Group was marginally significant, $F(1,16) = 3.64$, $p = .070$, $\eta_p^2 = .142$, and the Group by Hemisphere interaction was not significant, $F(1,16) = 0.15$, $p = .705$, $\eta_p^2 = .007$. For LOC, the main effect of Hemisphere was not significant, $F(1,18) = 1.16$, $p =$

.295, $\eta_p^2 = .061$, nor was the main effect of Group, $F(1,18) = 0.10$, $p = .76$, $\eta_p^2 = .005$, or the Group by Hemisphere interaction, $F(1,18) = 0.02$, $p = .905$, $\eta_p^2 = .001$. For V1, the main effect of Hemisphere was not significant, $F(1,18) = 0.91$, $p = .353$, $\eta_p^2 = .048$, nor was the main effect of Group, $F(1,18) = 2.91$, $p = .11$, $\eta_p^2 = .139$. The Group by Hemisphere interaction was also not significant, $F(1,18) = 2.89$, $p = .11$, $\eta_p^2 = .138$. Because FFA was only defined in the right hemisphere, the number of voxels was compared using an independent *t* test, which showed that WS participants (1517 voxels) and CA controls (1255 voxels) did not significantly differ (Cohen's $d = 0.22$, two-tailed $t(17) = –0.52$, $p = .608$). No main effects for hemisphere were found to be significant for ROI size, univariate, or multivariate analyses. Thus, bilateral ROIs are combined in all subsequent analyses.

Although none of the comparisons for size of each of the ROIs revealed a significant difference between the WS and CA groups, consideration of the trend of the dataset as a whole indicates that overall, the size of many of these functionally-defined regions may be smaller in WS, especially for the scene-selective areas of PPA ($p = .07$), RSC, and TOS. This is consistent with previous research, which has shown that individuals with WS show lower levels of activation for images of houses (O'Hearn et al., 2011; Sarpal, 2008). For right FFA however this difference is not evident, as the number of voxels is slightly numerically greater in WS participants than CA controls. This is also consistent with previous findings, which demonstrate that WS individuals show the same level of activation to face stimuli as chronological age matches (O'Hearn et al., 2011).

Although none of the differences for ROI size described above emerged as significant, I aimed to be especially mindful of the potential that WS participants may show less active voxels overall in response to spatial stimuli, as indicated by trends in our own data

and previous findings (Meyer-Lindenberg et al., 2004; O'Hearn et al., 2011; Sarpal, 2008). I use several methods to equate the number of voxels selected for analysis between the WS and CA groups (spherical ROIs for univariate analyses and constrained voxel sets for multivariate pattern analyses, methods described above), thus limiting potential group differences that may be due to differences in power.

Visual detection of changes in boundary height

A point of concern was whether WS participants would be able to visually detect the change in boundary height, particularly the small change between the Mat and Curb conditions. Perhaps if unprompted they simply would not notice or detect this change, and therefore potential differences observed at the neural level could simply be attributed to a matter of attentional focus. To test this, a follow-up behavioral study was conducted on a day separate from the scanning session. WS participants were seated before a computer screen, and watched as a stream of visual images was presented. To prevent overlap with the fMRI experiment, a separate set boundary images was created that exactly matched the Mat, Curb, and Wall dimensions of the fMRI stimulus set, but differed in color and pattern.

Before the experiment began, participants were given the following instructions: "You will see some different pictures of scenes. When the scene changes, clap your hands!" The experiment consisted of 4 runs. Each run consisted of 48 images that were each presented once per run. The timing of presentation of images and the duration of blanks between images matched the parameters of the fMRI experiment (time per image = 1 s, time between images = 0.2 s). In each run, there were 4 "small" changes (from Mat to Curb or Curb to Mat), and 4 "large" changes (Mat to Wall, Wall to Mat, Curb to Wall, and Wall to Curb). Thus, there were 8 instances per run where participants should detect that the scene

changed (32 times total over the course of 4 runs).

All WS participants accurately detected the change in boundary height on 100% of the trials (as did all CA controls). Thus, it may be inferred that differences in neural sensitivity are not a result of a failure to visually detect or notice changes in boundary height on behalf of the WS participants.

Univariate analyses

To investigate the response of each of the six ROIs of interest, a 2 × 3 mixed ANOVA was performed. The first factor was the between-subjects factor of Group (WS, CA), and the second factor was the within-subject factor of Boundary (Mat, Curb, Wall). To directly compare activity for the Mat vs. the Curb and activity for the Curb vs. the Wall within each group, planned comparison paired *t* tests were conducted. To correct for the multiple comparisons made within each ROI, the alpha level for significance was set to .025 (Bonferroni correction for the 2 comparisons performed within each group).

For the PPA (Figure 4.5), the main effect of Boundary was significant, $F(2,44) = 81.74$, $p < .001$, $\eta_p^2 = .788$, but the main effect of Group was not significant, $F(1,22) = 0.14$, $p = .717$, $\eta_p^2 = .006$. Interestingly, the interaction of Boundary and Group was significant, $F(2,44) = 4.87$, $p = .024$, $\eta_p^2 = .24$. The driver of this interaction may be due to the difference between the Mat and Curb; in the CA group there is a noticeable increase in activity from the Mat to the Curb, but for WS this difference appears to be absent. To explore this, I conducted a contrast by contrast interaction to consider Mat vs. Curb by WS vs. CA. This contrast was found to be significant, $F(2,44) = 12.55$, $p < .05$ (corrected for non-sphericity and for post-hoc comparisons using Scheffé's corrected critical *F* value of 6.42). This confirms that the difference between the Mat and Curb conditions was significantly greater for CA controls in

comparison to WS participants.

Planned *t* tests were conducted to investigate differences between conditions within each group. In CA controls, activity for the Curb was found to be significantly greater than the Mat, Cohen's $d = -0.67$, two-tailed $t(11) = -4.87$, $p < .001$, and activity for the Wall was significantly greater than the Curb, Cohen's $d = 0.75$, two-tailed $t(11) = -3.77$, $p = .003$. In contrast, for WS the only significant difference was found to be between the Curb and the Wall, Cohen's $d = 1.43$, two-tailed $t(11) = -9.56$, $p < .001$. Unlike CA controls, the difference between the Mat and the Curb was not found to be significant, Cohen's $d = -0.07$, two-tailed $t(11) = -0.76$, $p = .46$. These data support the hypothesis that the WS PPA shows an atypical response to the Curb. This indicates that the presence of minimal vertical structure is not encoded in the WS PPA in the same way as it is in CA controls. This difference is further explored using multivoxel pattern analysis below.

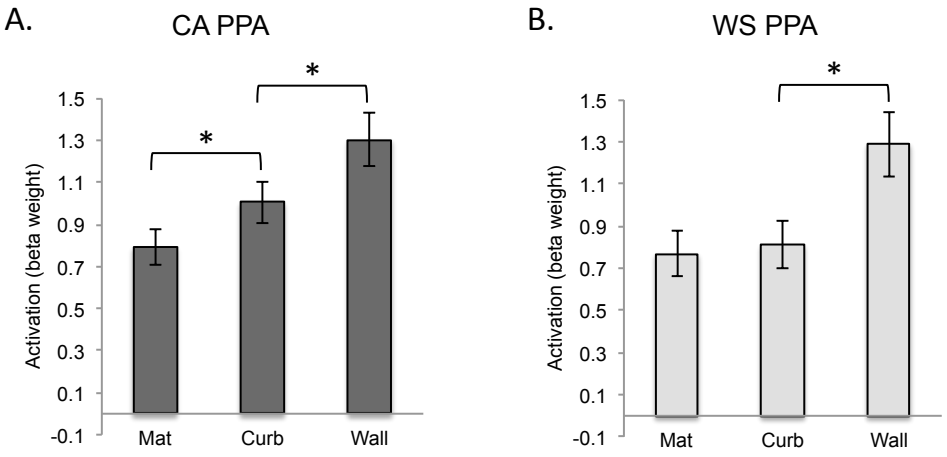

Figure 4.5: Beta weights for the PPA for each of the three boundary conditions in A) CA controls and B) WS participants. Error bars represent +/- standard error of the mean. Asterisks indicate significant difference between conditions, $p < .025$.

For RSC (Figure 4.6), the ANOVA revealed a significant main effect of Boundary, $F(2,32) = 19.56$, $p < .001$, $\eta_p^2 = .55$. The main effect of Group was not significant, $F(1,16) = 0.01$, $p = .917$, $\eta_p^2 = .001$, and the interaction of Boundary and Group was not significant, $F(2,32) = 0.35$, $p = .657$, $\eta_p^2 = .021$. RSC of CA controls did not show a significant difference between the Mat and Curb conditions, Cohen's $d = –0.36$, two-tailed $t(8) = –1.65$, $p = .14$, nor did RSC of WS participants, Cohen's $d = –0.07$, two-tailed $t(8) = –0.90$, $p = .397$. For both groups, the difference between the Curb and Wall was significant, CA: Cohen's $d = –0.73$, two-tailed $t(8) = –2.94$, $p = .019$, WS: Cohen's $d = 0.45$, two-tailed $t(8) = –2.76$, $p = .023$. These findings indicate that in both CA and WS, RSC is sensitive to a large amount of vertical structure, but not slight variations as introduced by the transition from the Mat to the Curb.

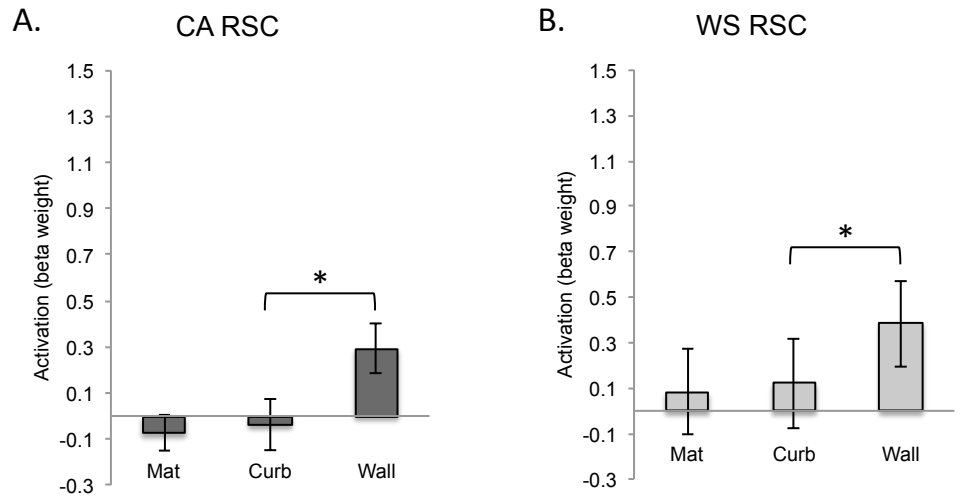

Figure 4.6: Beta weights for RSC for each of the three boundary conditions in A) CA controls and B) WS participants. Error bars represent +/- standard error of the mean. Asterisks indicate significant difference between conditions, $p < .025$.

The response of TOS, another scene-selective area, was also investigated. For this region (Figure 4.7), the main effect of Boundary was significant, $F(2,32) = 19.36$, $p < .001$, $\eta_p^2 = .547$. The main effect of Group was not significant, $F(1,16) = 0.58$, $p = .459$, $\eta_p^2 = .035$,

nor was the Boundary by Group interaction, $F(2,32) = 0.23$, $p = .755$, $\eta_p^2 = .014$. In CA controls, TOS activity for the Mat vs. the Curb was not significant, Cohen's $d = –0.14$, two-tailed $t(8) = –0.72$, $p = .491$. This comparison was also not significant in the WS group, Cohen's $d = –0.10$, two-tailed $t(8) = –0.72$, $p = .493$. Both groups however did show a significant difference between the Curb and the Wall, CA: Cohen's $d = 0.48$, two-tailed $t(8) = –3.53$, $p = .008$, WS: Cohen's $d = 0.73$, two-tailed $t(8) = –4.38$, $p = .002$. This overall pattern matches what was found for RSC; the small amount of vertical structure present in the Curb condition is not sufficient to distinguish it from the Mat.

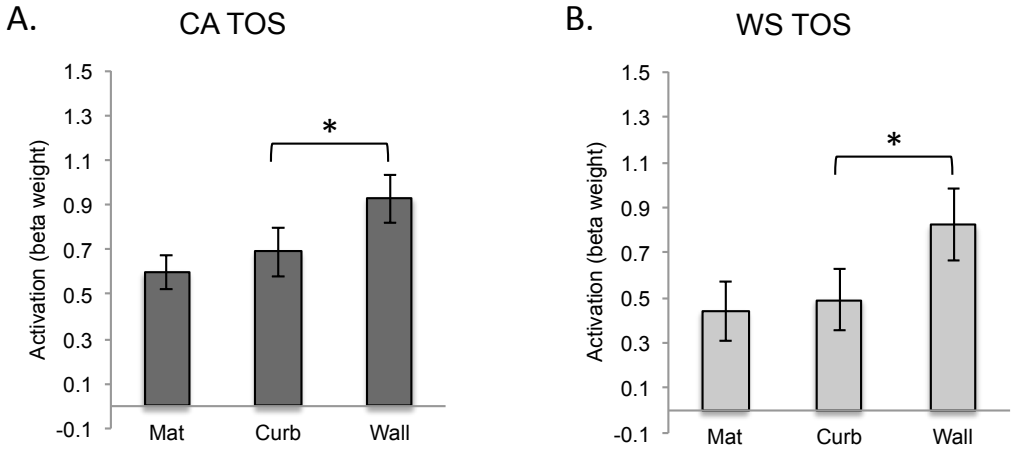

Figure 4.7: Beta weights for TOS for each of the three boundary conditions in A) CA controls and B) WS participants. Error bars represent +/- standard error of the mean. Asterisks indicate significant difference between conditions, $p < .025$.

The responses of two functionally defined regions that are not scene-selective were also considered (LOC and FFA). Evaluation of the activity of these regions enables one to infer whether activity of PPA, RSC and TOS reflect uniquely scene-specific responses, or if these patterns are observable in other high-level visual areas, and thus may be due to differences between the boundary stimuli that are not scene-specific. In LOC (Figure 4.8), the main effect of Boundary was not significant, $F(2,36) = 1.53$, $p = .233$, $\eta_p^2 = .078$, nor was

the main effect of Group, $F(1,18) = 2.09$, $p = .166$, $\eta_p^2 = .104$, or the Boundary by Group interaction, $F(2,32) = 1.50$, $p = .240$, $\eta_p^2 = .077$. The difference between the Mat and Curb was not significant for either the CA or WS group, CA: Cohen's $d = –0.18$, two-tailed $t(9) = –0.89$, $p = .395$, WS: Cohen's $d = –0.23$, two-tailed $t(9) = –1.56$, $p = .153$. The difference between the Curb and Wall was also not significant for either group, CA: Cohen's $d = –0.23$, two-tailed $t(9) = 1.28$, $p = .227$, WS: Cohen's $d = –0.12$, two-tailed $t(9) = –0.71$, $p = .497$. While PPA, RSC, and TOS all showed a main effect of Boundary in both CA and WS, LOC did not. Because LOC does not distinguish between any of the boundary conditions, this provides supporting evidence for the conclusion that the observed responses of PPA, RSC, and TOS (which all distinguished between at least some of the boundary conditions) are in fact reflective of scene-specific processing.

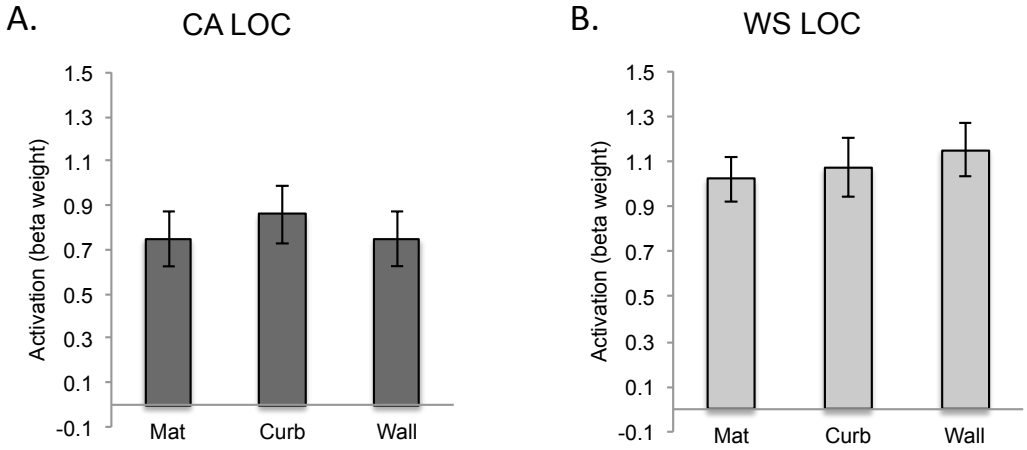

Figure 4.8: Beta weights for LOC for each of the three boundary conditions in A) CA controls and B) WS participants. Error bars represent +/- standard error of the mean.

In FFA (Figure 4.9), the main effect of Boundary was not significant, $F(2,44) = 2.04$, $p = .148$, $\eta_p^2 = .085$, nor was the main effect of Group, $F(1,22) = 0.19$, $p = .664$, $\eta_p^2 = .009$. The Boundary by Group interaction was also not significant, $F(2,44) = 0.18$, $p = .814$, $\eta_p^2 = .008$. No significant differences between the conditions emerged for either the Mat vs. the

Curb, CA: Cohen's $d = -0.07$, two-tailed $t(11) = -0.54$, $p = .598$, WS: Cohen's $d = -0.11$, two-tailed $t(11) = -1.03$, $p = .326$, or for the Curb vs. the Wall, CA: Cohen's $d = -0.05$, two-tailed $t(11) = -0.44$, $p = .669$, WS: Cohen's $d = -0.05$, two-tailed $t(11) = -0.55$, $p = .591$. These data, like those for LOC, provide further evidence that the activity of PPA, RSC and TOS in response to the boundary conditions is indicative of the processing of visual information that is scene-specific.

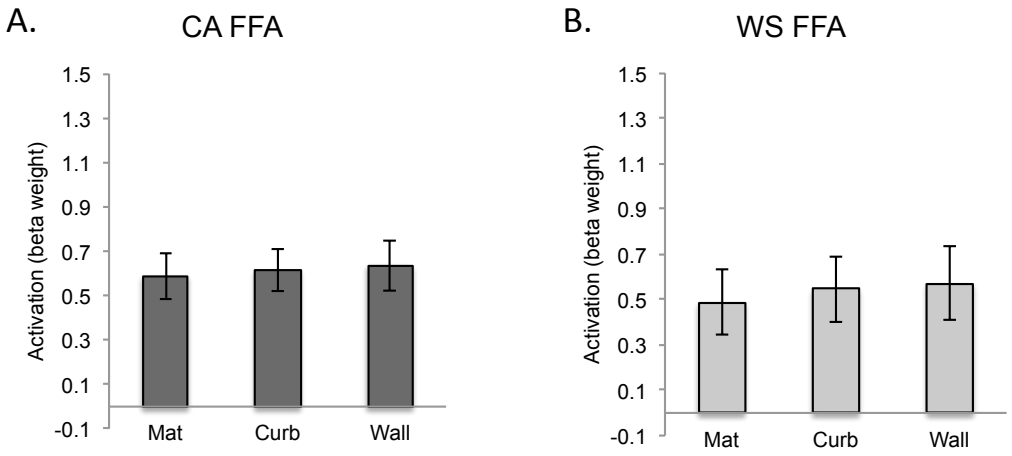

Figure 4.9: Beta weights for FFA for each of the three boundary conditions in A) CA controls and B) WS participants. Error bars represent +/- standard error of the mean.

Lastly, I considered the response of primary visual area V1 (Figure 4.10). The ANOVA revealed a significant main effect of Boundary, $F(2,36) = 93.01$, $p < .001$, $\eta_p^2 = .838$. The main effect of Group was not significant, $F(1,18) = 0.06$, $p = .818$, $\eta_p^2 = .003$, and the Boundary by Group interaction was not significant, $F(2,36) = 0.31$, $p = .614$, $\eta_p^2 = .017$. V1 of CA controls showed a significant difference between the Mat and Curb, Cohen's $d = -0.66$, two-tailed $t(9) = -2.98$, $p = .01$, and also between the Curb and Wall, Cohen's $d = 1.95$, two-tailed $t(9) = -5.89$, $p < .001$. V1 of WS participants also showed a significant difference between both the Mat and Curb, Cohen's $d = -0.44$, two-tailed $t(9) = -2.98$, $p = .016$, and the Curb and Wall, Cohen's $d = 2.76$, two-tailed $t(9) = -9.89$, $p < .001$. These data indicate that

early visual processing of scene stimuli does not differ between the WS and CA groups, and thus differences that are observed in high-level visual areas (e.g., PPA) are not attributable to differences at the earliest stages of visual processing.

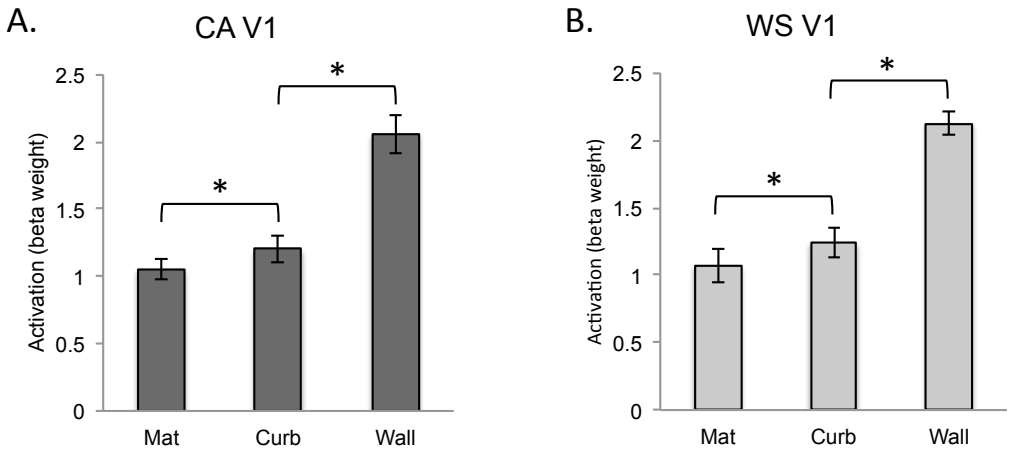

Figure 4.10: Beta weights for V1 for each of the three boundary conditions in A) CA controls and B) WS participants. Error bars represent +/– standard error of the mean. Asterisks indicate significant difference between conditions, $p < .025$.

Pixel analysis

It should be noted that the pattern of univariate response demonstrated by V1 appears similar to that which was observed for the PPA of CA controls: there is a significant step-wise increase from Mat, to Curb, to Wall. This similarity raises the question that the step-wise pattern observed in the PPA may merely be a recapitulation of what is processed by V1. That is, sensitivity to a slight amount of 3D structure is not a true characterization of the PPA's representation of the spatial boundary *per se*, but rather is driven by the low-level visual difference between the Curb and Mat stimuli, which is calculated in V1. However, I maintain that V1 responds more directly to increases in the raw amount of visual information from Mat to Curb to Wall, while the PPA performs a qualitatively different type of processing that reflects its specific sensitivity to scene structure.

To test this, I obtained a count of the number of pixels that belong to the region of the stimulus images that portray the boundary and ground (not including the gray background). The Mat included 19552 pixels, the Curb included 24664 pixels, and the Wall included 96591 pixels. Correlations were next computed between univariate response of the PPA and V1 and the amount of pixels in the corresponding conditions. The resulting *r* values were high for both regions; for the PPA, CA: $r = .82$; WS: $r = .98$, and for V1, CA: $r = .98$; WS: $r = .99$. For CA controls, the correlation value obtained for V1 was significantly greater than that obtained for the PPA, $z = 3.13$, $p = .01$. However, the correlation values did not differ for WS, $z = 0.11$, $p = .45$.

Overall, this provides evidence that the response of V1 very closely corresponds to the amount of visual information portrayed in a particular boundary condition. Note that the *r* value for V1 is nearly equivalent to 1 for both groups, suggesting an almost perfect correlation between its univariate response and the amount of pixels in the stimulus images. The PPA's response also shows a high correlation to the amount of visual information, but in CA controls, this value is significantly lower than V1. Note that in particular, the response to the Curb in the CA PPA is characterized by a disproportionate increase in activity that is nearly equivalent to the increase from the Curb to the full Wall—a greater response is elicited by the Curb in CA PPA than what would be expected by pixel content alone.

This finding is further supported by the work of Ferrara & Park (2014), in which it was found that in TD adults, PPA's specific response to the Curb condition is erased when the stimulus images are turned upside down. This indicates that the PPA is selectively sensitive to the ecological validity of vertical boundaries that rise from the ground up. The response of V1 to the Curb condition was not affected by whether the stimuli were presented

upside down or right-side up, further supporting the inference that V1's discrimination of the boundary conditions is driven by the amount of visual information that varies from one condition to the next, and thus is not affected by the spatial location of this information within the stimulus image.

The pixel analysis revealed that the WS PPA did not differ from V1 in terms of correlation to the amount of visual content that increases from one boundary condition to the next. A disproportionate response to the slight increase of vertical structure in the Curb is not evident in WS as it is in CA controls. However, this is not to imply that the WS PPA is literally recapitulating the same type of processing that is accomplished by primary visual area V1. Recall that the WS PPA was functionally defined by its selective response of scenes – objects, just as it was for CA controls. Thus it may be inferred that the WS PPA does demonstrate at least some degree of specific sensitivity to scenes.

Discussion

Analysis of ROI activity in response to each of the three boundary conditions revealed largely similar patterns between WS individuals and CA controls, with one important difference. In the PPA of healthy adults, it was found that the response to the three different boundary conditions showed a clear step-wise pattern from Mat, to Curb, to Wall, replicating the findings of Ferrara & Park (2014). There is impressive sensitivity to the structural change from the Mat to the Curb, even though just a tiny bit of vertical structure is added, this is picked up on by the PPA and it shows a significantly different response. For this scene region, grounded minimal vertical structure plays a critical role, just as plays a critical role for geometric reorientation by young children. This bears a striking resemblance to the gradient pattern of geometric search made by children across boundary conditions that

was observed in the reorientation task. Thus, in both the behavior of young children and this particular scene region, these collective findings demonstrate that the Wall condition has the strongest effect, followed by the Curb, followed by the Mat.

In contrast, the PPA of WS participants did not show a response that significantly differed between the Mat and the Curb. This suggests that this region's sensitivity to the presence of 3D vertical boundary information is affected by the WS genetic deficit. Likewise, WS participants did not demonstrate a gradient of geometric search across the boundary conditions in behavioral reorientation, instead showing no increase in geometric search from the Mat array to the Curb. It is notable however that the overall activity of the WS PPA was not reduced relative to CA controls, as levels of response to the Mat and Wall stimuli were nearly identical. Thus, there appears to be a specific abnormality in the response of the WS PPA to a slight amount of 3D vertical structure. This is further explored using MVPA in the subsequent section.

The univariate response of another scene-selective area, RSC, did not differ between WS and CA controls. Previous research suggests that RSC's response is driven by the functional consequences that a particular boundary presents (e.g., is it one that may be easily crossed or not) (Ferrara & Park, 2014). Based upon these data, it does not appear that this representation is atypical in WS—both the Mat and the Curb are boundaries that are easy to cross, and thus RSC shows the same level of response to both types of boundaries (in both WS participants and CA controls). The full Wall in contrast is a functionally limiting boundary, and consequently RSC treats it as significantly different from the Mat and the Curb (again in both WS and CA controls).

The response of a third scene area, TOS, also did not distinguish between the Mat and

Curb conditions in either WS participants or CA controls. Less is known about this region's specific role in scene processing, but these data suggest that unlike PPA, it does not represent fine-grained differences between a lack of vertical structure (the Mat), and a slight vertical increase (the Curb). Previous research has shown that like PPA, TOS is sensitive to the spatial layout of scenes (e.g., open or closed) (Dilks et al., 2013). The findings presented here however indicate that TOS's representation of spatial layout is not as finely tuned to the aspect of scene structure that boundaries specifically contribute. TOS is also sensitive to the left-right orientation of scenes (Dilks et al., 2011). This suggests that TOS may be involved in representing the navigational properties of scenes, as the path you would travel to move through a scene changes when its orientation is flipped. If this is so, it would follow that TOS should not discriminate between the Mat and Curb boundaries, which present similar navigational consequences, as discussed above in relation to the representation of RSC.

To evaluate early visual processing of the boundary conditions, our analyses included consideration of the response of primary visual area V1. In both CA controls and WS participants, the activity of this region showed a very strong correspondence to the amount of visual information (quantified by number of pixels) within each condition. These results demonstrate that early visual processing of these stimuli is not impaired in WS. Further supporting evidence comes from the behavioral discriminability task that was conducted outside the scanner, where it was found that WS participants were just as accurate as CA controls in detecting changes in boundary height (even for the small change between the Mat and the Curb).

Divided ROI analysis for anterior and posterior PPA

To further explore sensitivity of the PPA, the functionally localized region was

divided into 4 equalized portions (PPA 1, PPA 2, PPA 3, and PPA 4, Figure 4.11). Although the entire PPA in WS did not show a significant difference in response between the Mat and the Curb, it is possible that perhaps one specialized sub-region may show this difference when analyzed separately. Just as was done for the other ROIs, each PPA sub-region was submitted to a GLM to obtain an estimated effect size of the univariate response for each boundary condition. To compare activity for the Mat vs. the Curb and activity for the Curb vs. the Wall within each PPA sub-region, planned comparison paired *t* tests were conducted. To correct for the multiple comparisons made within each ROI, the alpha level for significance was set to .025 (Bonferroni correction for the 2 comparisons performed within each ROI). Below I first review results for the divided PPA of CA controls, followed by WS participants.

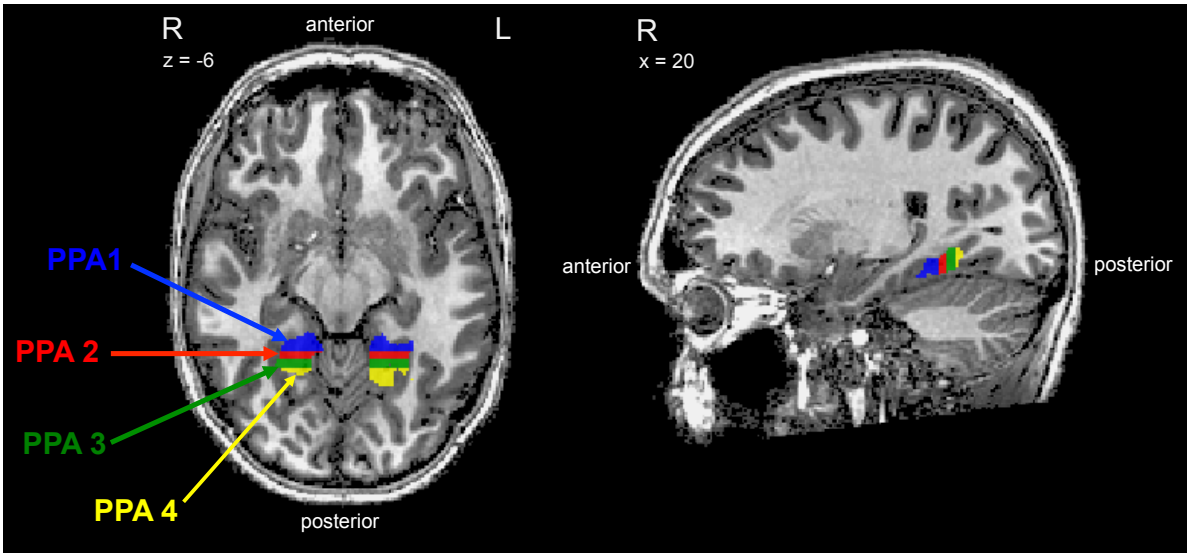

Figure 4.11: An example of PPA 1, PPA 2 (anterior) and PPA 3, PPA 4 (posterior) in one representative subject.

In CA controls (Figure 4.12), three divided sub-regions of the PPA replicated the step-wise pattern from Mat, to Curb, to Wall that had been observed in analysis of the entire

ROI. PPA 2, 3, and 4 all showed significant differences between the Mat and the Curb (PPA 2: Cohen's $d = –0.45$, two-tailed $t(11) = –3.13$, $p = .01$; PPA 3: Cohen's $d = –0.51$, two-tailed $t(11) = –3.38$, $p = .006$; PPA 4: Cohen's $d = –0.74$, two-tailed $t(11) = –4.06$, $p = .002$), as well as between the Curb and the Wall (PPA 2: Cohen's $d = –0.69$, two-tailed $t(11) = –4.78$, $p = .001$; PPA 3: Cohen's $d = –0.86$, two-tailed $t(11) = –4.45$, $p = .001$; PPA 4: Cohen's $d = –0.79$, two-tailed $t(11) = –5.50$, $p < .001$). Although PPA 1 did show a significant difference between the Curb and the Wall, Cohen's $d = –0.52$, two-tailed $t(11) = –4.86$, $p = .001$, it did not for the Mat and the Curb, Cohen's $d = –0.28$, two-tailed $t(11) = –2.03$, $p = .07$ (Figure 4.12).

To directly compare the response of the most anterior portion of PPA (PPA 1) to the most posterior portion (PPA 4), a 2 × 3 mixed ANOVA was performed for PPA sub-region (PPA 1, PPA 4) and Boundary (Mat, Curb Wall). This revealed a main effect of PPA sub-region, $F(1,22) = 12.19$, $p = .002$, $\eta_p^2 = .36$, as well as Boundary, $F(2,44) = 37.66$, $p < .001$, $\eta_p^2 = .63$. The interaction of these two factors was also significant, $F(2,44) = 3.14$, $p = .05$, $\eta_p^2 = .13$. This indicates that the most anterior and most posterior portions of PPA in CA controls differ in terms of magnitude of response to the boundary conditions.

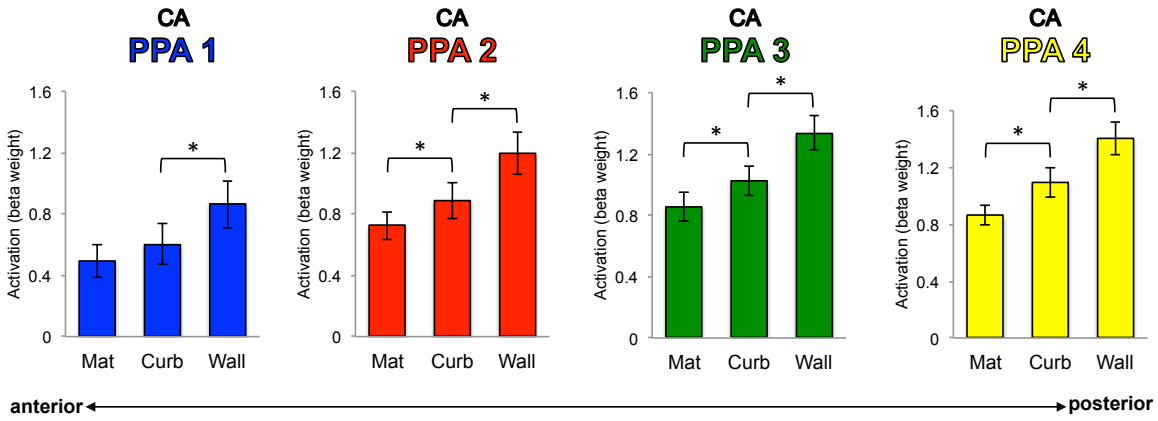

Figure 4.12: Beta weights for PPA 1, PPA 2, PPA 3 and PPA 4 of CA controls for each of the three boundary conditions. Error bars represent +/– standard error of the mean. Asterisks indicate significant difference between conditions, $p < .025$.

In WS participants (Figure 4.13), none of the sub-regions of the PPA showed a significant difference between the Mat and Curb (PPA 1: Cohen's $d = –0.13$, two-tailed $t(11) = –1.66$, $p = .13$; PPA 2: Cohen's $d = –0.18$, two-tailed $t(11) = –1.19$, $p = .26$; PPA 3: Cohen's $d = –0.23$, two-tailed $t(11) = –1.75$, $p = .11$; PPA 4: Cohen's $d = –0.17$, two-tailed $t(11) = –1.96$, $p = .08$). All sub-regions however did show significant differences between the Curb and the Wall, just as had been found for the entire ROI (PPA 1: Cohen's $d = –0.63$, two-tailed $t(11) = –4.24$, $p = .001$; PPA 2: Cohen's $d = –1.11$, two-tailed $t(11) = –5.98$, $p < .001$; PPA 3: Cohen's $d = –0.83$, two-tailed $t(11) = –5.06$, $p < .001$; PPA 4: Cohen's $d = –0.78$, two-tailed $t(11) = –5.90$, $p < .001$). A 2 × 3 ANOVA for PPA sub-region (PPA 1, PPA 4) and Boundary (Mat, Curb, Wall) revealed main effects of Boundary, $F(2,44) = 54.44$, $p < .001$, $\eta_p^2 = .71$, and PPA sub-region, $F(1,22) = 70.59$, $p < .001$, $\eta_p^2 = .76$, as had been found for CA controls. However, unlike CA controls, the interaction between PPA sub-region and Boundary was not significant, $F(2,44) = 1.19$, $p = .32$, $\eta_p^2 = .05$.

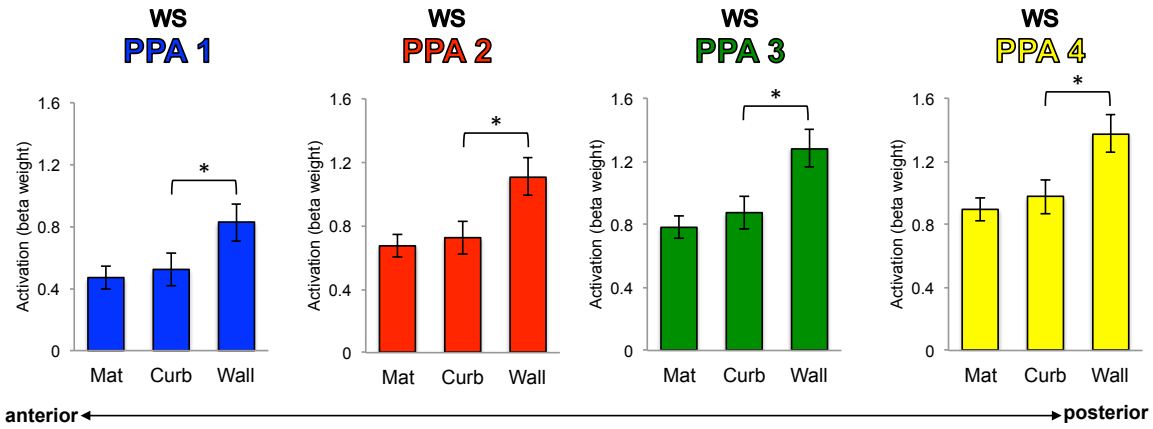

Figure 4.13: Beta weights for PPA 1, PPA 2, PPA 3 and PPA 4 of WS participants for each of the three boundary conditions. Error bars represent +/– standard error of the mean. Asterisks indicate significant difference between conditions, $p < .025$.

There is not yet a common method for functionally defining sub-regions of the PPA. Here a split-half analysis was performed twice over to explore differences between the most anterior (PPA 1) and most posterior (PPA 4) portions of the PPA. In CA controls, it was found that the most anterior portion of PPA did not reveal the same sensitivity for the Mat vs. Curb as the other sub-regions; the univariate response to these conditions was not significantly different for these two conditions in PPA 1. This finding adds to the growing body of evidence that the PPA is not a homogenous region, but rather shows functional differences along the anterior/posterior axis (Arcaro et al. 2009; Baldassano et al. 2013; Bar & Aminoff, 2003). Functional connectivity analyses have shown that the anterior aspect of PPA correlates more strongly at rest with RSC, while posterior PPA correlates more strongly at rest with LOC (Baldassano et al. 2013; Kravitz et al., 2011b). In a sense this fits with our findings; anterior PPA shows functional connectivity to RSC, and here I find that the most anterior portion of PPA (PPA 1) mirrors the pattern observed in the univariate response of RSC—both do not distinguish between the Mat and Curb conditions.

The divided analyses further characterize the WS atypical response observed of the

PPA region as a whole. It is possible that analysis of the entire ROI may have obscured the potential sensitivity of one sub-region, which when analyzed independently would in fact show a significant difference in response between the Mat and the Curb. One such sub-region was not identified. However, the *t* test comparisons did reveal one intriguing marginally significant result, which is that the sub-region that came the closest to significant discrimination between the Mat and Curb was the very most posterior portion of PPA (PPA 4) at $p = .07$. This is speculative as the result is only marginally significant, but this suggests that the WS PPA may also follow an anterior/posterior functional division that is similar to CA controls. However, overall sensitivity is reduced, and thus the Mat vs. Curb comparison does not emerge as significant.

Whole-brain analysis

Exploratory whole-brain analyses were conducted to see if areas outside the defined ROIs would show sensitivity to the different boundary conditions. Furthermore, there may be areas in the WS brain that, although not scene-selective in the typical brain, may in fact show sensitivity to the differences in vertical height present in the boundary conditions. Two contrasts were conducted: (1) Mat < Curb and (2) Curb < Wall. If a particular brain region shows sensitivity to the slightest amount of boundary structure, it would be revealed by the Mat < Curb contrast. Conversely, if dramatic differences in vertical height are required for a brain region to distinguish between two boundary conditions, it would be revealed by the Curb < Wall contrast. Below I first describe results for CA controls, followed by results for the WS participants.

The contrast for Mat < Curb revealed two significant clusters in CA controls in the right and left lingual gryus (Table 4.2, Figure 4.14.A). The lingual gyrus is part of the

functionally defined PPA, which is found in the posterior part of the parahippocampal gyrus and extends to the lingual gyrus. Thus, this finding is consistent with our univariate results, in which the PPA in CA controls showed significant differences in activity between the Mat and the Curb. The fact that this most posterior portion of PPA is identified by the random effects analysis also supports the divided PPA analysis described above, which indicates that sensitivity to the difference between the Mat and the Curb is more functionally localized to the posterior portion. No clusters were found that indicated sensitivity for Mat > Curb (which would have been indicated by blue clusters in Figure 4.14 below).

The Curb < Wall contrast revealed several regions in CA controls that are also consistent with our univariate findings (Figure 4.14.B). Just as was revealed by the Mat < Curb contrast, a significant cluster is found in the lingual gyrus (e.g., posterior portion of the PPA). Notably, right and left RSC clusters are only significant for this contrast and not the Mat < Curb contrast, mirroring the univarite response in which RSC distinguishes between the large difference in vertical height between Curb and Wall, but not the small difference between Mat and Curb. Additional early visual areas revealed by this contrast (right and left middle occipital gyrus, right and left occipital cortex) show evidence of processing of the low-level visual differences between the Curb and Wall conditions. No significant clusters of activity were found that indicated sensitivity to Curb > Wall (again, this would have been revealed by blue clusters of activity).

Table 4.2: Names of regions showing significance for the Mat < Curb or Curb < Wall contrasts in CA controls. MNI coordinates for the peak voxel within each cluster are listed, along with the magnitude of the peak *T* value and average *T* value, the number of voxels within a cluster, and the count of subjects who showed the same region in individual whole-brain analyses.

Region	Average peak MNI coordinates (*x, y, z*)	Peak *T* value	Average *T* value	Number of voxels	Number of participants
Mat < Curb (Figure 4.14.A)					
R lingual gyrus	26, -73, -13	6.81	5.29	263	11/12
L lingual gyrus	-28, -76, -16	6.05	5.01	128	10/12
Curb < Wall (Figure 4.14.B)					
R parahippocampal gyrus	23, -43, -13	8.95	5.61	426	12/12
R lingual gyrus	26, -73, -16	9.89	5.51	387	11/12
R retrosplenial cortex	17, -52, 8	6.89	4.58	170	11/12
L retrosplenial cortex	-16, -67, 14	7.49	4.64	161	10/12
R middle occipital gyrus	8, -97, 17	14.73	6.01	1509	11/12
L middle occipital gyrus	-7, -94, 14	10.82	5.93	1094	12/12
R occipital cortex	5, -85, -4	12.41	6.41	1833	12/12
L occipital cortex	-10, -76, -4	10.58	6.06	1926	12/12

Random effects analysis, $p < .001$

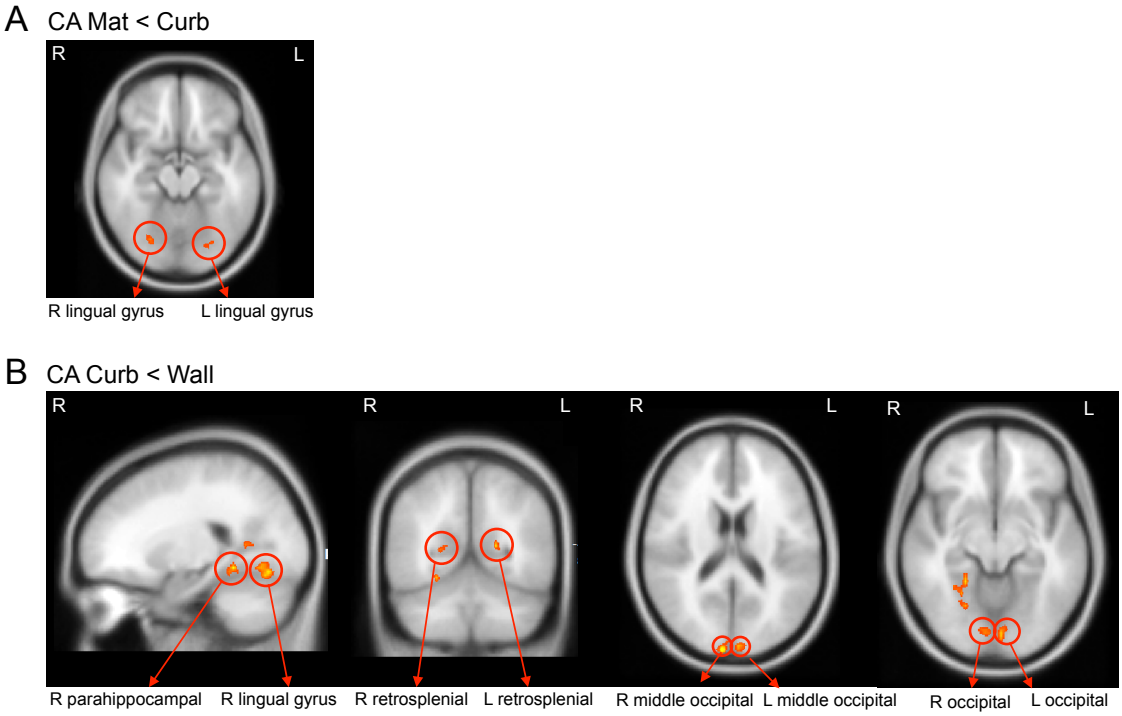

Figure 4.14: Regions identified via whole-brain analysis (random effects analysis, p < .001, cluster threshold = 4 voxels) are shown on the MNI EPI template. Names of regions are marked with arrows below each figure. A) Regions showing significance for the Mat < Curb contrast in CA controls. B) Regions showing significance for the Curb < Wall contrast in CA controls.

For WS participants (Table 4.3, Figure 4.15), the whole-brain analysis did not reveal any significant clusters for the Mat < Curb contrast. This corresponds with the univariate response of the WS PPA, which did not significantly distinguish between the Mat and Curb. This finding further suggests that the fine-grained sensitivity to the Curb that was observed in CA controls has not shifted to another region in the atypical WS brain, and hence it does not appear that this processing is being accomplished elsewhere. No clusters were found indicating sensitivity to Mat > Curb.

The Curb < Wall contrast showed many of the same areas in WS participants as CA controls. Right and left parahippocampal clusters were identified in the WS group, which corresponds with the difference in univariate response of the WS PPA between the Curb and the Wall. Similarly, a cluster for left RSC was also found. It is speculative, but comparison of the WS and CA data indicates that sensitivity to boundaries of this kind may right-lateralized to a greater degree in the typical brain; no left lingual gyrus or parahippocampal activity was found for CA controls for the Curb < Wall contrast, while no right RSC was found for WS participants. Right-lateralization of scene-selective regions has been found in previous whole-brain analyses of TD adults (Park et al., 2015).

It is important to note that for the Curb < Wall contrast, all early visual areas identified in CA controls are also identified in WS (right and left occipital cortex and middle occipital gyrus). This provides further evidence that the groups do not differ in this respect, and that the WS lack of sensitivity to the Curb is not due to atypicalities in early visual processing.

Table 4.3: Regions showing significance for the Curb < Wall contrast in WS participants. MNI coordinates for the peak voxel within each cluster are listed, along with the magnitude of the peak *T* value and average *T* value, the number of voxels, and the count of subjects who showed the same region in individual whole-brain analyses.

Region	Average peak MNI coordinates (*x, y, z*)	Peak *T* value	Average *T* value	Number of voxels	Number of participants
Mat < Curb					
No areas found					
Curb < Wall (Figure 4.15)					
R parahippocampal gyrus	26, -52, -7	6.88	5.14	349	11/12
L parahippocampal gyrus	-28, -58, -10	8.01	5.39	575	10/12
L retrosplenial cortex	-19, -61, 5	7.92	5.52	168	9/12
R middle occipital gyrus	14, -97, 23	7.12	5.04	848	12/12
L middle occipital gyrus	-13, -103, 14	6.54	5.11	779	11/12
R occipital cortex	5, -91, -7	7.89	5.31	1318	12/12
L occipital cortex	-4, -88, -10	9.39	5.72	1350	12/12

Random effects analysis, $p < .001$

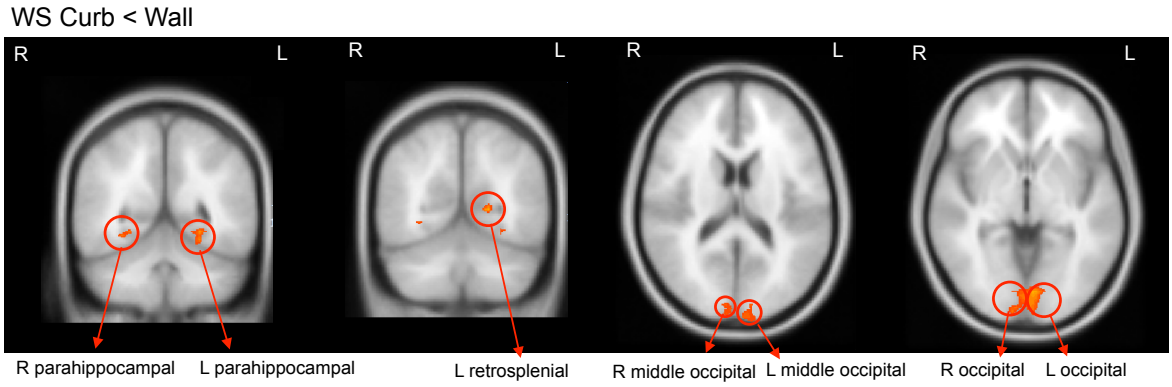

Figure 4.15: Regions identified via whole-brain analysis (random effects analysis, p < .001, cluster threshold = 4 voxels). Names of regions are marked with arrows below each figure. Regions showing significance for the Curb < Wall contrast in WS participants are shown (none identified for the Mat < Curb contrast).

Collectively, the whole-brain analyses largely replicate at the level of individual participants for both WS and CA groups, as a large proportion of participants show the same areas in individual fixed-effects whole-brain analyses as were revealed by the group analysis (see Table 4.2 and Table 4.3). In the individual analyses, no WS participants were found to show significant clusters of activation for the Mat < Curb contrast.

Multivoxel pattern analysis

Comparison of the levels of univariate response indicate that, in contrast to CA controls, the WS PPA is not sensitive to the difference in vertical boundary structure between the Mat and Curb conditions. However, univariate analyses may not be sensitive enough to capture the nature of the underlying representation of a particular region. This point was first demonstrated by Haxby and colleagues, who showed that information that was not evident from univariate analyses could be decoded from patterns of fMRI activation across voxels (Haxby et al., 2001). Thus, MVPA is also employed, which is sensitive to not only overall activation levels, but also the spatial pattern of multivoxel activity within an ROI.

Classification accuracy

Percent correct classification for each ROI was calculated as the average SVM performance across participants within each group (Figure 4.16). If the specific neural pattern for the Curb condition is one that can be uniquely differentiated from the Mat and the Wall, the classifier will be able to predict the correct label of "Curb." Alternatively, if there are strong similarities between brain patterns for different conditions, then there will be no particular pattern that can be matched to a condition, and the classifier will fail.

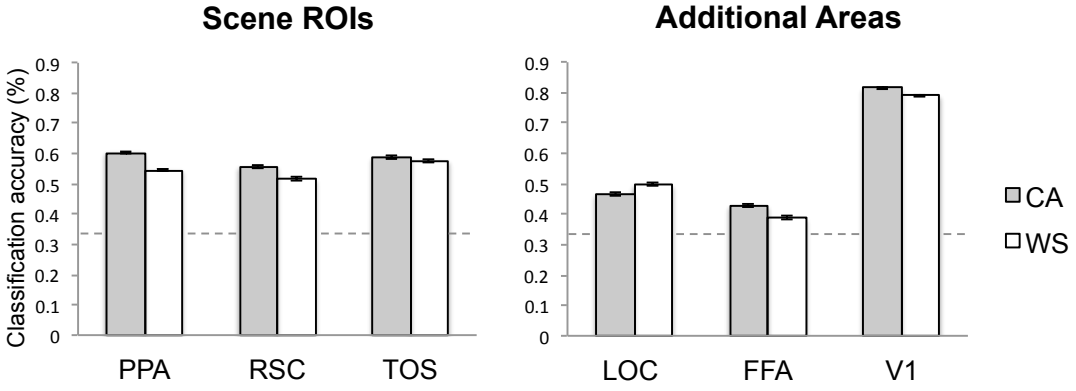

Figure 4.16: Average classification accuracy (percentage) in scene ROIs (PPA, RSC, TOS) and additional ROIs of interest (LOC, FFA, V1), shown for both the CA and WS groups. Chance (33%) is indicated by the dashed line. Error bars indicate +/– standard error of the mean.

Classification accuracy in all of the ROIs for both participant groups was significantly above chance (33%). For CA controls, PPA, RSC, TOS, LOC, FFA, and V1 had respective classification accuracies of 60% (Cohen's $d = 2.63$, two-tailed $t(11) = 9.12$, $p < .001$); 56% (Cohen's $d = 2.56$, two-tailed $t(11) = 8.87$, $p < .001$); 59% Cohen's $d = 1.91$, two-tailed $t(10) = 6.34$, $p < .001$); 50% (Cohen's $d = 1.44$, two-tailed $t(11) = 4.99$, $p < .001$); 39% (Cohen's $d = 3.14$, two-tailed $t(11) = 3.41$, $p = .006$); and 79% (Cohen's $d = .98$, two-tailed $t(10) = 10.40$, $p < .001$). For WS participants, PPA, RSC, TOS, LOC, FFA, and V1 had respective classification accuracies of 55% (Cohen's $d = 2.21$, two-tailed $t(11) = 7.65$, $p < .001$); 52% (Cohen's $d = 2.49$, two-tailed $t(8) = 7.46$, $p < .001$); 58% (Cohen's $d = 2.33$, two-tailed $t(8) = 6.99$, $p < .001$); 50% (Cohen's $d = 1.86$, two-tailed $t(9) = 5.89$, $p < .001$); 39% (Cohen's $d = 0.97$, two-tailed $t(11) = 3.37$, $p < .001$); and 79% (Cohen's $d = 3.23$, two-tailed $t(9) = 20.32$, $p < .001$). (These tests use the Bonferroni corrected alpha = .008 for the 6 comparisons made within each group.) Further *t* tests revealed no significant differences between the CA and WS groups for each respective ROI (all *p*s > .28).

Classification errors

For the PPA of the WS group, comparison of the levels of univariate response did not show a significant difference between the Mat and Curb conditions. This stands in striking contrast to CA controls, whose activity patterns of the PPA did distinguish the slight amount of vertical structure present in the Curb. However, univariate analyses may not be sensitive enough to capture the nature of the underlying representations in this region (Haxby et al., 2001). Analysis of the patterns of confusion errors made by an MVPA classifier can reveal whether a particular brain region represents different boundary conditions as similar or distinct from one other (Park et al., 2011). To test the nature of boundary representation

within a particular ROI, hypothetical confusion matrices were established. Values were assigned to each of the 9 cells in a 3 × 3 matrix to reflect different hypotheses.

Figure 4.17.A illustrates the hypothesis that the Mat, Curb, and Wall conditions are uniquely represented as distinct from one another. This matrix would be observed if brain patterns are sensitive in distinguishing the amount of 3D vertical structure that varies across the conditions. Figure 4.17.B illustrates the hypothesis that the brain patterns from an ROI are insufficient to distinguish between the Mat and Curb (all given a value of 1 in the model), while the high degree of vertical structure in the Wall stands apart (given a value of 2). Figure 4.17.C illustrates a case in which the slight amount of vertical structure included in the Curb is sufficient to render it indistinguishable from patterns associated with the Wall. Lastly, Figure 4.17.D is a model of the case where the Mat and Wall have similar patterns, and the Curb is unique. (Based on the reorientation literature there is not supporting evidence for this model, but its inclusion allows for the testing of all possible combinations.)

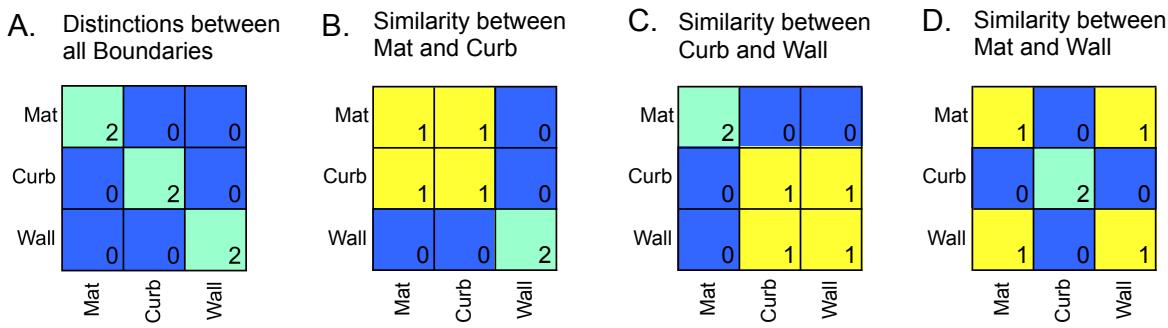

Figure 4.17: Illustration of the four confusion matrices set up to test different hypotheses about the representation of boundaries within the ROIs.

To quantify whether the multivoxel patterns of the ROIs fit with a particular model, correlations were computed between values assigned to the hypothetical confusion matrices and the data obtained from the confusion matrix of each ROI. This correlation was computed for each participant. To test for significance across participants, correlation coefficients (*r)*

for each participant were transformed using the Fisher's *z* transformation to represent the normally distributed *z* variable. These values were then entered into ANOVAs and *t* tests, as described below.

The correlation between CA PPA (Figure 4.18.A) and the model that represents Distinctions between all Boundaries was found to be significant, $r = .87$, $p = .004$, as was the correlation to the model that represents Similarity between Mat and Curb, $r = .77$, $p = .02$. WS PPA (Figure 4.18.A) showed significant correlations to these two models as well, $r = .72$, $p = .03$ and $r = .79$, $p = .02$, respectively. Correlations for the two remaining models were not significant for either group (all *p*s > .11). To compare the two groups, the *z*-transformed correlation values were submitted to a 2 × 2 mixed ANOVA. The first factor was the between-subjects factor of Group (WS, CA), and the second factor was the within-subject factor of Model (Distinction between all Boundaries, Similarity between Mat and Curb). The ANOVA yield a non-significant main effect of Model, $F(1,22) = 0.88$, $p = .49$, $\eta_p^2 = .04$, as well as Group, $F(1,22) = 0.82$, $p = .38$, $\eta_p^2 = .04$. However, the Model by Group interaction was significant, $F(1,22) = 5.35$, $p = .03$, $\eta_p^2 = .20$. Planned comparison *t* tests revealed that the PPA of CA controls had a significantly higher correlation to the model for Distinction between all Boundaries over the model for Similarity between Mat and Curb (Cohen's $d = 0.23$, two-tailed $t(11) = 2.60$, $p = .02$), but this was not true for the PPA of WS participants (Cohen's $d = –0.82$, two-tailed $t(11) = –0.59$, $p = .57$) (Figure 4.18.B).

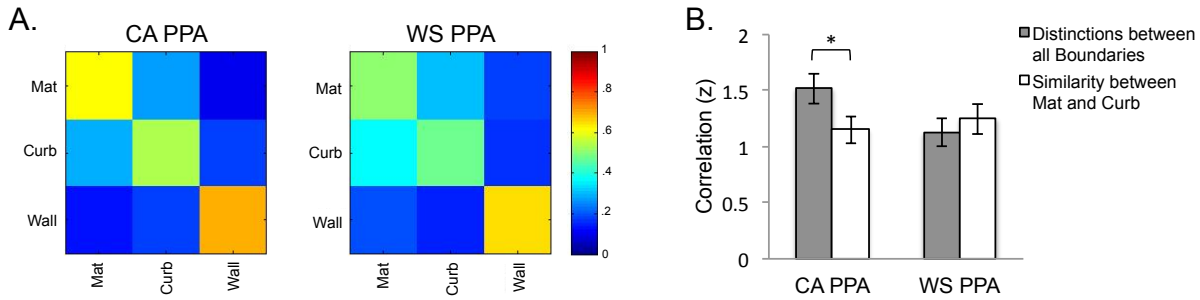

Figure 4.18: A) Confusion matrices generated by the classifier when trained separately on the neural patterns obtained from the PPA of CA controls and the PPA of WS participants. B) The PPA of CA controls shows a higher correlation to the model that represents distinct classification of all three boundary conditions. Error bars indicate +/– standard error of the mean. Asterisk indicates a significant difference between the two models, $p < .05$.

For RSC, the correlation between this ROI in CA controls (Figure 4.19.A) and the model that represents Distinctions between all Boundaries was significant, $r = .73$, $p = .03$, as was the correlation to the model that represents Similarity between Mat and Curb, $r = .81$, $p = .009$. WS RSC (Figure 4.19.A) also showed significant correlations to these two models, $r = .74$, $p = .04$ and $r = .76$, $p = .02$, respectively. Correlations for the two remaining models were not significant for either group (all ps > .19). The ANOVA yielded a significant main effect of Model, $F(1,19) = 4.97$, $p = .04$, $\eta_p^2 = .21$. The main effect of Group was not significant, $F(1,19) = 0.82$, $p = .38$, $\eta_p^2 = .11$, but the Model by Group interaction was significant, $F(1,19) = 4.50$, $p = .04$, $\eta_p^2 = .19$. Planned comparison t tests revealed that RSC of CA controls had a significantly higher correlation to the model for Similarity between Mat and Curb over the model for Distinction between all Boundaries (Cohen's $d = 1.01$, two-tailed $t(8) = –2.20$, $p = .05$), but this was not true for RSC of WS participants (Cohen's $d = 0.02$, two-tailed $t(8) = –0.09$, $p = .93$) (Figure 4.19.B).

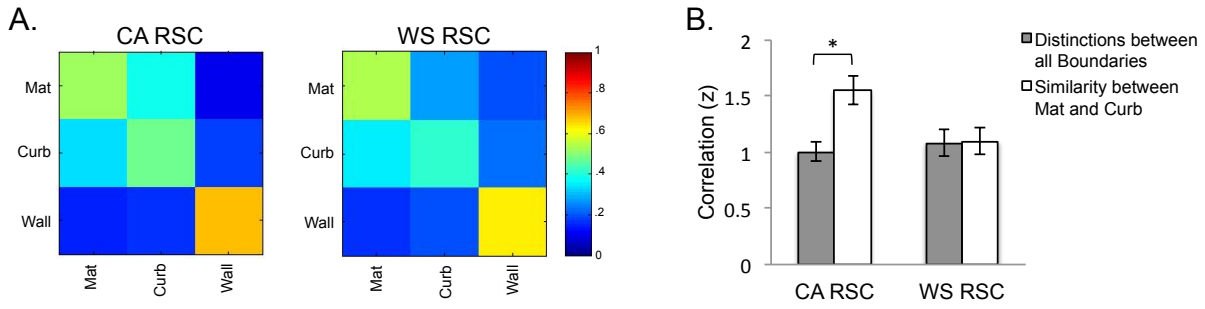

Figure 4.19: A) Confusion matrices generated by the classifier when trained separately on the neural patterns obtained from RSC of CA controls and RSC of WS participants. B) RSC of CA controls shows a higher correlation to the model that represents similarity between the voxel pattern of activity for the Mat and Curb conditions. Error bars indicate +/– standard error of the mean. Asterisk indicates a significant difference between the two models, $p <$ .05.

The four other ROIs were also analyzed (TOS, LOC, FFA and V1) to explore which hypothetical representational model showed the strongest correlation to the confusion matrices generated by the classifier when trained on the neural data from these ROIs (see Appendix A). No differences emerged between the WS and CA groups. Thus, I turn to further focus on potential qualitative differences between the PPA and RSC within each participant group.

Based upon the previous findings of Ferrara and Park (2014), I predicted that in CA controls, the PPA and RSC would qualitatively differ in their representation of boundaries. To directly compare these ROIs within each participant group, two-way within-subject ANOVAs were conducted (ROI (PPA, RSC) × Model (Distinctions between all Boundaries, Similarity between Mat and Curb). For CA controls, the ANOVA revealed a significant interaction of ROI and Model, $F(1,8) = 17.82$, $p = .001$, $\eta_p^2 = .62$, which indicates that the contribution of the models significantly differs between PPA and RSC (Figure 4.20.A). The main effects of ROI, $F(1,8) = 0.28$, $p = .61$, $\eta_p^2 = .03$, and Model, $F(1,8) = 0.28$, $p = .61$, $\eta_p^2 = .03$, were not significant. Thus, for CA controls the activity patterns of these ROIs reflect qualitatively different representations: the PPA is sensitive to each type of boundary

condition as different from one other, while RSC is not sensitive to the minimal vertical cue present in the Curb, showing consistent confusion between the Mat and Curb conditions.

Comparing the two ROIs in WS (Figure 4.20.B), the ANOVA did not reveal a significant main effect of ROI, $F(1,8) = 1.18$, $p = .31$, $\eta_p^2 = .13$, or Model, $F(1,8) = 0.66$, $p = .44$, $\eta_p^2 = .08$. Unlike CA controls, the ROI by Model interaction was not significant, $F(1,8) = 0.25$, $p = .63$, $\eta_p^2 = .03$. These analyses indicate that in WS, PPA and RSC do not have the same representational biases for boundaries as found in CA controls.

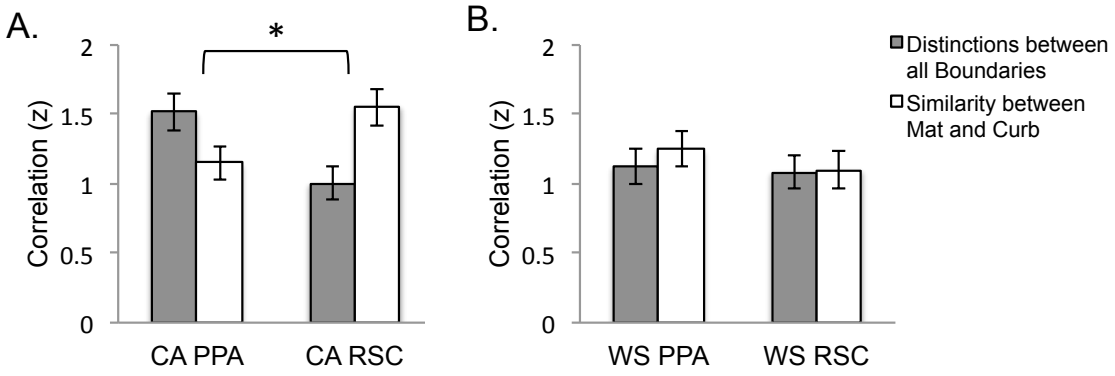

Figure 4.20: A) CA controls show a significant interaction between ROI (PPA, RSC) and Model (Distinctions between all Boundaries, Similarity between Mat and Curb). The asterisk indicates the significant interaction. B) This interaction is not observed in WS.

Lastly, to directly compare differences between PPA and RSC in the WS and CA groups, a repeated-measures ANOVA for ROI (PPA, RSC) × Model (Distinctions between all Boundaries, Similarity between Mat and Curb) with Group (WS, TD) as a between-subjects factor was run. The main effect of ROI was not significant, $F(1,19) = 1.44$, $p = .25$, $\eta_p^2 = .07$, nor was the main effect of Model, $F(1,19) = 0.75$, $p = .40$, , $\eta_p^2 = .04$ or Group, $F(1,19) = 0.99$, $p = .33$, $\eta_p^2 = .05$. The interactions of ROI by Group ($F(1,19) = 0.28$, $p = .60$, $\eta_p^2 = .02$), Model by Group ($F(1,19) = 0.006$, $p = .94$, $\eta_p^2 = .00$), and ROI by Model ($F(1,19) = 3.34$, $p = .09$, $\eta_p^2 = .15$) were not significant. However, the interaction of ROI by Model by Group was significant, $F(1,19) = 7.50$, $p = .013$, $\eta_p^2 = .28$, which further highlights that the

PPA and RSC show stronger correlations to one model over the other in CA controls, but these differences are not present in WS.

Discussion

Collectively, these analyses demonstrate that the PPA and RSC of WS individuals do not have the same representational structure as those of CA controls. In CA controls, it was found that the spatial pattern of activity in the PPA correlates most strongly with the representational model for unique classification of all three boundary conditions. RSC instead shows the highest correlation to the representational model for unique classification of the Wall condition. These findings replicate those of Ferrara and Park (2014); in TD adults, the PPA is finely tuned to detect the presence of minimal vertical structure, while RSC requires the full boundary of the Wall. This demonstrates that in the healthy adult brain, boundaries are a structural aspect of scenes that are encoded by high-level scene areas to form distinctly different and complementary representations. For one area (PPA), minimal vertical structure is key, just as it is key for the geometric reorientation of young children. For another area (RSC), these results and additional follow-up experiments (Ferrara & Park, 2014) suggest that the functional affordance of a boundary is key.

In contrast, the spatial patterns of activity in the PPA and RSC of WS individuals did not show differentiation between the two hypothetical models. For the PPA, this coincides with its univariate pattern of response; the WS PPA does not distinguish between the Mat and the Curb in terms of overall activation, and using MVPA it was found that the spatial pattern of voxels does not show as strong of a correlation to the model that represents Distinction between all Boundaries as CA controls. Collectively, these data identify a WS neural deficit in representation of minimal amounts of 3D vertical boundary structure. This

representation is known to be crucially important for reorientation in the real world, and in the case of typical development, appears very early in life (Lee & Spelke, 2008; 2011). In Experiment 1, we found that WS individuals did not reorient geometrically by the Curb array. In Experiment 2, we find a corresponding neural pattern, in that the PPA does not appear to be sensitive to the vertical boundary of the Curb.

Based upon the univariate data alone, RSC of WS participants appeared to match the response profile of RSC in CA controls. In both groups, RSC univariate activity does not distinguish between the Mat and the Curb, and only treats the full Wall as significantly different from the other two conditions. However, MVPA reveals that the spatial pattern of activity of the voxels in this scene region differs between WS individuals and CA controls. WS RSC shows significant correlations to the two hypothetical models of interest, but unlike CA controls, the correlation to the model for Similarity between Mat and Curb is no higher than the correlation to the model for Distinctions between all Boundaries. This indicates a WS neural deficit in the function of this region as well, in that its voxel pattern of response to boundaries of different heights is not as spatially distinct as CA controls. The connection of this neural atypicality to behavioral performance is not as directly tested in the present study as for the PPA (sensitivity to Curb; reorientation by Curb array). However, it is possible that atypical function of RSC in WS individuals is related to their impairment in a variety of navigation and wayfinding tasks (Atkinson et al., 2002; Farran et al., 2010; 2012; Lakusta et al., 2010; Nardini et al., 2008).

Analyses of data from Experiment 1 and Experiment 2

Experiment 2 reveals atypical neural sensitivity to boundaries in WS, specifically in the scene-selective regions of the PPA and RSC. I now turn to explore whether these neural

differences correspond to atypical behavioral patterns in the reorientation task, specifically at the level of individual participants.

Univariate activity and geometric performance

At the group level, findings from Experiment 2 reveal that the WS PPA does not distinguish between the Mat and Curb conditions when these images are visually presented in the scanner. This parallels behavioral reorientation performance in Experiment 1; as a group, WS participants search randomly amongst the four corners of the Curb array and do not demonstrate sensitivity to its geometric structure. However, there were 3 individuals with WS who searched geometrically on at least 3 out of the 4 trials in the Curb array. This may be attributable to chance, but may also indicate that these individuals did demonstrate true geometric sensitivity to the geometry of the Curb array. I hypothesized that these participants in particular may reveal a relationship between the magnitude of the difference between the PPA's activity for the Curb vs. the Mat and geometric response in the Curb condition (Figure 4.21). That is, for those participants who were able to reorient by the geometry of the Curb, activity of the PPA may show a greater degree of differentiation between the Mat and Curb conditions. To test this, a partial correlation was conducted (controlling for whole-brain volume[10] and age) between PPA activity for the Curb minus the Mat and the proportion of geometric search made in the Curb array. This correlation was not significant, $r(8) = -.50$, $p = .139$. (This relationship was also non-significant for CA controls, $r(8) = -.28$, $p = .426$.)

[10]Although it was found that the WS and CA groups did not significantly differ in terms of whole-brain volume, this variable was entered as a covariate in the partial correlations to account for its potential influence on behavioral measures, particularly for the WS group.

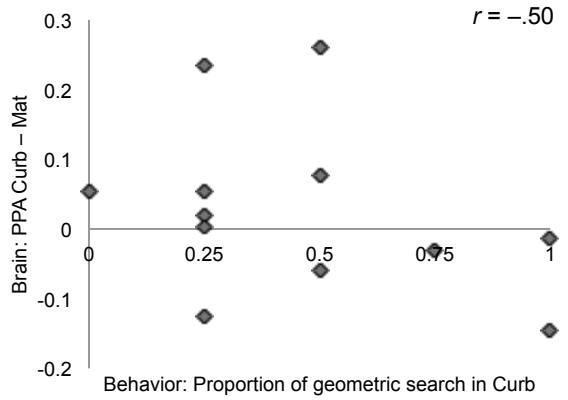

Figure 4.21: Correlation between the difference in activity of the WS PPA between the Mat and Curb conditions and the proportion of geometric searches made by WS participants in the Curb array of the reorientation experiment.

Additional partial correlations were performed to explore the potential relationship between an ROI's level of response and geometric search in reorientation. For example, is there a positive relationship between the amount of activity that the PPA shows in response to the Mat condition, and the proportion of geometric search made by individuals in the Mat reorientation array? This relationship was tested for the three scene-selective ROIs (PPA, RSC, and TOS). No correlations were found to be significant for either the WS or CA group (all *p*s > .18). This relationship was also tested for LOC, reasoning that perhaps in WS this object-selective region may show greater involvement in navigation tasks, given their spatial deficit. This correlation was not significant for either the WS or CA group (all *p*s > .21).

ROI size and geometric performance

A second hypothesis is the possibility that there may be a relationship between geometric reorientation and the size of an ROI. Because the ROIs were functionally defined, their size is indicative of the contiguous number of voxels that passed the threshold of $p < .0001$ (see Methods for further details). Perhaps the correlating neural factor is not the overall amount of activity of an ROI, but the expanse of neural tissue that it occupies. To explore

this, partial correlation analyses were conducted (again controlling for age and whole-brain volume) between ROI size (number of voxels) and the proportion of geometric search made in each of the three reorientation conditions. No significant correlations were found for either the WS or CA group (all *p*s > .22) for PPA, RSC, TOS, or LOC.

Discussion

The correlation analyses do not provide strong support of the hypothesis of specific connections between reorientation by the small Curb structure and the PPA's discrimination of the slight Curb boundary in visually-presented scenes. This finding has several potential explanations. First, it is possible that this conjectured relationship simply does not hold. Alternatively, it is also possible that within this limited subject pool, there is an insufficient number of data points to reveal statistically significant correlations. Perhaps if more participants were tested who reliably reoriented geometrically in the Curb condition, differences in PPA sensitivity would be found between these participants and those who searched randomly. Additionally, it may be the case that the reorientation task, with only four trials and thus only four observable data points, is too coarse of a measure to reveal potential connections to neural data. In future research, more complex navigation measures (e.g., number of incorrect turns through a large scale environment) may be sensitive enough to reveal connections between the performance of a person with WS and their corresponding patterns of neural activity. Individual subject-based results of this kind have been found for TD adults (e.g., Furman et al., 2014).

CHAPTER 5: GENERAL DISCUSSION

In this thesis, I propose that 3D vertical structure is a crucial factor for what qualifies a boundary as such. Behavioral and neuroimaging methods are used to investigate how this criteria is realized in both real-world navigation and the brain. The use of boundaries in reorientation acts as a litmus test for the representation of boundaries at the neural level. I hypothesize that if scene-selective visual areas are unable to encode crucial geometric differences between boundaries (i.e., the difference between the Mat and Curb conditions), the ability to reorient by these types of boundaries (i.e., a flat Mat and a 5 cm Curb) will show impairment. As an example of spatial deficit due to genetic deletion, people with WS offer a unique test case for this relationship.

Experiment 1 tests TD four- and six-year-olds, individuals with WS, and TD CA controls in three different types of reorientation arrays: a Mat, a Curb, and full Walls. All TD groups reoriented geometrically in both the Curb and Wall arrays. In contrast, individuals with WS did not reliably reorient in accord with the geometry of the Curb, and only did so for the Wall. This demonstrates a specific impairment in sensitivity to minimal boundary structure in this population. An additional finding of Experiment 1 further characterizes the developmental trajectory of reorientation by abstract 2D boundaries: although four-year-olds did not reorient by the geometry of the Mat (replicating Lee & Spelke, 2011), six-year-olds constrained their searches to the geometrically appropriate corners in this array.

Experiment 2 tests neural sensitivity in individuals with WS and CA controls to artificial scenes that contain three different types of boundaries: a flat Mat, and slight Curb, and a full Wall. In CA controls, we find a neural correlate to the fine-grained sensitivity to minimal vertical structure that was observed in behavioral reorientation. Using both

univariate and multivoxel analyses, the PPA shows acute sensitivity to the presence of grounded 3D vertical structure (the Curb). We also find evidence supporting that what defines a boundary qualitatively differs for different scene regions in the TD brain; RSC does not distinguish between the Mat and Curb, only treating the functionally limiting Wall as distinct. For WS, activity of the PPA does not distinguish between the Mat and Curb. In contrast to the complementary representation of boundaries by PPA and RSC in the TD brain, MVPA revealed that these representations are less distinct and are not biased towards one region over the other in WS.

In Chapter 2, I reviewed key areas in the brain involved in navigation and scene processing (Figure 5.1). How do these collectively support the representation of boundaries for use in reorientation? This is surely a topic of ongoing research, but here I attempt to assemble the body of relevant findings to paint a picture of the underlying neural network and potential points of malfunction in WS.

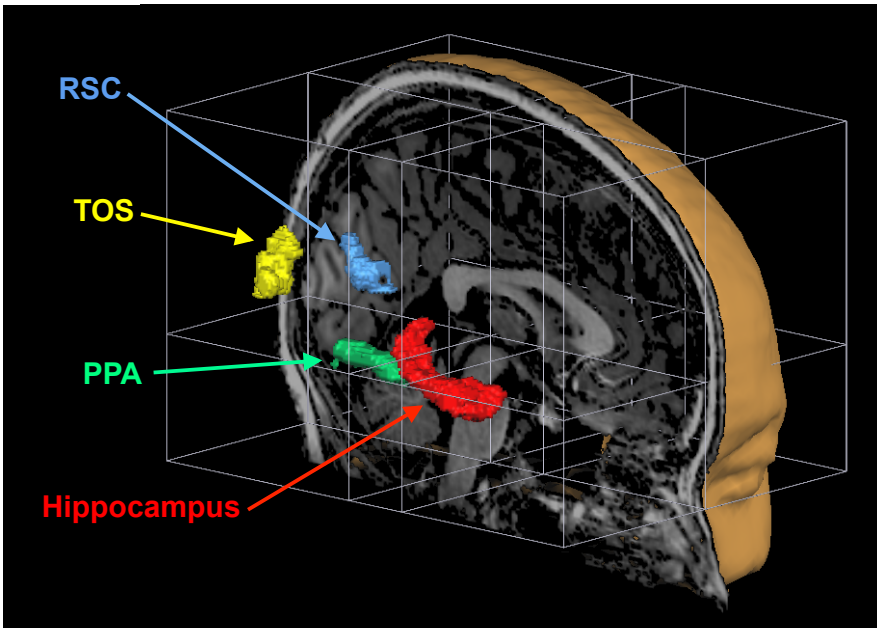

Figure 5.1: Brain areas involved in scene processing.

At an early stage in encoding, there exists a direct connection between boundaries in the environment and their processing at the neural level: BVCs in the subiculum of the hippocampal formation (Lever et al., 2009; Sharp, 2006) that fire when the organism is facing a given direction at a certain distance from specific walls. In addition, border cells, found in the entorhinal cortex and the parasubiculum, fire when an animal is close to or at a boundary in the environment, regardless of its directional orientation (Savelli et al., 2008). Lever and colleagues found that low-ridge boundaries (similar to the Curb boundary in the present research) anchor BVC firing (Lever et al., 2009). BVC activity has been observed early in life (Wills et al., 2010), just as reorientation by a 2 cm curb has been observed at early points in human development (Lee & Spelke, 2011). This provides the first possible indicator of potential malfunction in the developmental disorder of WS: perhaps the specific tuning of BVCs (and possibly border cells) is not fine-grained enough to fire in response to minimal boundary cues. This tuning could be more coarsely defined, such that full wall boundaries are detectable (by which WS individuals reoriented geometrically), but a small curb is not.[11]

The transfer of input between border cells, BVCs, and place cells is the subject of ongoing research. Broadly however, it is understood that BVCs provide input to place cells, which are located in the hippocampus proper (O'Keefe & Burgess, 1996; Burgess et al., 2000; Hartley et al., 2000). The hippocampus is a known site of atypicality in WS, in terms of both structure and function (Meyer-Lindenburg et al., 2005; 2006). This is another possible locus of WS impairment in the encoding of environmental boundaries; perhaps the tuning of BVCs and border cells is intact, but once this information is passed on to the

[11] This could be tested in genetically modified mice, whose chromosome 5 contains the analog of the affected WS region of chromosome 7 in humans (Segura-Puimedon et al., 2014).

hippocampus, it becomes degraded and consequently impairs behavioral reorientation.

The findings presented in this thesis point to another region in the brain that is key to the representation of vertical boundary structure. The case of WS illustrates a link between representation of the Curb boundary by the PPA and use of this type of boundary in reorientation: when the PPA does not demonstrate sensitivity to the Curb, geometric reorientation suffers. Research with monkeys indicates that the parahippocampal gyrus (corresponding to cytoarchitectonically defined parahippocampal areas TH, TF, and TFO in monkeys) receives strong projections from the hippocampus and parietal cortex (Kravitz et al., 2011b). It is possible that the strength of these connections could be weaker in WS. A similar result has been found for people with congenital prosopagnosia, who demonstrate normal cortical activation in the inferior temporal cortex to faces, but weakened projections between anterior and posterior inferior temporal cortex, as shown by DTI (Thomas et al., 2009). Likewise in WS, the problem may lie in how the information is passed on in the transfer of boundary information from BVCs, to the hippocampus, to the PPA. The connections between the PPA and the hippocampus could be the point of breakdown in this chain, and as a result, the WS PPA does not receive sufficient input to demonstrate a significant boost in response to the Curb condition in comparison to the Mat.

It was however observed that the WS PPA level of activity for the Wall was no different from controls. If general weakness in the connections between the PPA and hippocampus is the site of impairment, we may have expected to see an overall reduction in response to these scene stimuli (i.e., reduced response to the Wall condition relative to CA controls). It is possible that the WS impairment in boundary representation may be confined to the PPA itself, rather than its connections to other areas. Monkey neurons in area TFO

(corresponding to human parahippocampal gyrus) have large receptive fields and a weak foveal bias (Larsson & Heeger, 2006). This larger receptive field and spatial bias correspond to the known functional properties of the human PPA, which represents the peripheral spatial boundary information of scenes (Kravitz et al., 2011a; Park et al., 2011) and local scene geometry (Epstein et al., 2003). Perhaps the receptive fields of WS PPA neurons do not match these tuning characteristics—they may be even more broadly tuned than in the TD case. This broader tuning may be sufficient to detect large amounts of peripheral boundary structure, but when only a slight amount of boundary structure is present, it is not detected. As a result, this reduction in sensitivity requires a more salient difference in vertical height if the boundary is to be encoded. Another potential connection to PPA atypicality in WS is the use of landmarks in navigation. fMRI research with healthy adults indicates that this area is likely involved in this process, as it represents both the stability and navigational relevance of objects (Janzen and van Turennout 2004; Schinazi & Epstein, 2010; Troiani et al., 2012). People with WS show atypical use of landmarks in reorientation (Ferrara & Landau, under review) and route learning (Farran et al., 2010). This additionally supports the conclusion that the function of this region is atypical in WS.

In further exploration of the structure and function of the PPA, the region was divided into four subdivisions along the anterior-posterior axis. In CA controls, sensitivity to the difference in vertical structure between the Mat and Curb was biased towards posterior sub-regions. Functional connectivity analyses have shown that the more anterior aspect of PPA correlates more strongly at rest with RSC (Baldassano et al., 2013; Kravitz et al., 2011b). This fits nicely with our findings, which show that the response patterns of the most anterior portion of PPA resembles that of RSC; it does not distinguish between the Mat and the Curb.

Although none of the PPA sub-regions in WS showed sensitivity to this difference, a marginally significant distinction was found in the most posterior aspect of PPA. This suggests that the WS PPA follows an anterior/posterior functional division that is similar to CA controls, but overall sensitivity to boundary structure is dampened.[12]

RSC is another scene-selective visual area that these findings revealed to be atypical in WS. Connectivity studies in humans using both DTI and fMRI have shown that the parahippocampal region is connected to RSC (Caspers et al., 2011; Kahn et al., 2008; Libby et al., 2012; Rushworth et al., 2006). Thus, MVPA differences observed in WS RSC could be a reflection of atypical boundary information that it receives via its connections to PPA. However, a large body of research suggests that RSC's representation of scenes is distinctly different from that of the PPA (e.g., Epstein, 2008), and therefore RSC's representation of scene boundaries is likely not solely a product of input it receives from the PPA. RSC is situated on the medial surface, near the transition zone between the PPA along the ventral stream and medial dorsal stream regions (Kobayashi & Amaral 2003; Kravitz et al. 2011b). This positioning relative to other regions, along with its observed response properties, broadly supports the current view that RSC is involved in situating a given scene within the broader spatial environment (Park et al., 2015; Epstein 2008). How might sensitivity to environmental boundaries play a role in this process? Recent research indicates that RSC codes for both location and facing direction, defined on the basis of fixed elements of the local environment. These location and direction codes were also found to generalize across geometrically similar local environments (i.e., environments that had similar structural

[12] Future studies with additional types of stimuli (e.g., objects, real-world scenes, following the work of Baldassano and colleagues) will help to further characterize whether response of the functional subunits of the WS PPA resembles those of TD individuals.

configurations of their boundary walls) (Marchette et al., 2014). This indicates that RSC anchors our "internal compass" to local topographical features, perhaps the most salient of which are environmental boundaries. Thus, RSC likely plays a crucial role in the accomplishment of reorientation: when an organism has lost its sense of direction and must recover from a state of disorientation, it uses cues from the external environment (e.g., the geometry of boundaries) to reset its sense of position and direction. These data and those of previous research (Ferrara & Landau, under review; Lakusta et al., 2010) demonstrate that this is a specific point of behavioral impairment in WS, of which RSC may be the underlying neural correlate. When WS individuals do not have to recover their sense of heading direction (i.e., remain oriented), they are able to locate a target quite accurately (on 92% of trials (Lakusta et al., 2010)). Thus, the issue is not in maintaining a sense of orientation or representation of the target location over time, but rather in using the geometry of the environment to recover orientation once it has been lost.

As suggested by previous research, an additional role of RSC may be representation of the functional affordance of boundaries (i.e., whether the particular boundary presents a significant impediment to the viewer's future navigation) (Ferrara & Park, 2014). If the representation of boundaries in WS RSC is atypical, does this then imply that the representation of functional obstacles to navigation is generally impaired as well? The findings presented here for RSC demonstrate that univariate activity in response to a functionally limiting boundary (the Wall) did not differ from that of CA controls. Based upon this, one may conclude that the functional representation of boundaries is intact in WS. However, MVPA results indicated that the spatial pattern of activity across voxels in this region was not as distinct as those of CA controls. A similar result has been observed in

Autism. While reading stories portraying accidental vs. intentional harm, adults with Autism did not differ from controls in magnitude of response in the right temporo-parietal junction (a theory of mind region). However, MVPA of this region revealed that unlike controls, adults with Autism did not show reliable and distinct patterns of response across voxels for intentional vs. accidental harms (Koster-Hale, Saxe, Dungan, & Young, 2013). Likewise, the RSC MVPA data indicate that the representation of the functional affordance of boundaries is not as finely tuned as those of CA controls.[13]

The final region to consider in discussion of the scene network is TOS. Less is known about the specific characteristics of this area, but research using TMS has shown that it plays a causal role in scene perception (Dilks et al., 2013). Due to its positioning that is more posterior than PPA or RSC, Dilks et al. (2013) speculate that TOS is involved in earlier stages of scene processing. In the present research, TOS (identified bilaterally in 9 out of 12 WS individuals), shows perhaps the largest discrepancy between the WS and CA groups in terms of size (Figure 4.4), although this difference was not significant. However this suggests the possibility that representation of boundaries in this area is impaired in WS, and this impaired representation would then be passed on to higher levels of scene processing (PPA and RSC). This could contribute to the atypical representations in these ROIs that were observed, which do not reflect the distinctions of those in CA controls.

Importantly, our analyses permit us to identify some aspects of neural processing that are an unlikely basis of WS impairment. Both univariate and multivoxel analyses indicate that the response of primary visual area V1 to the different boundary conditions does not

[13] This could be tested in future research by investigating neural and behavioral sensitivity in WS to the varied boundaries of increasing heights shown in Figure 2.10 (Ferrara & Park, 2014). I predict that WS RSC will not show as distinct of a categorical difference in response between stimulus heights 5 and 6, as was found for TD adults (see Chapter 2 for further discussion of this finding).

differ between the WS and CA groups. Other aspects of early visual processing also appear typical in WS: Palomares and colleagues have demonstrated adult-like thresholds among WS people in tasks requiring the integration of oriented elements into global forms (Palomares, Landau & Egeth, 2009). Olsen et al. (2009) has also shown that V1 size does not differ between WS individuals and chronological or mental age matched controls. These data suggest that damage to early visual processes cannot account for the WS PPA's lack of sensitivity to the Curb condition. Furthermore, the results of a behavioral detection experiment outside the scanner demonstrate that individuals with WS are just as accurate as TD adults in visually discriminating the changes in boundary height in these stimuli. Thus, it is unlikely that the lack of response to the Curb condition in Experiment 2 is attributable to low attention or low-level visual processing differences of the WS group.

Evidence of similar neural sensitivity between WS and CA controls speaks to a broader point in the literature. In this thesis, I have taken the perspective that the unusual case of WS may be used to inform our understanding of the usual. However, others have argued that atypical cases of development fundamentally change cognitive structure (Karmiloff-Smith, 1998; Karmiloff-Smith 2007), and thus drawing comparisons to typical development and adult TD individuals is an uninformative exercise in comparing "apples to oranges" (Landau & Hoffman, 2012). Karmiloff-Smith argues that cases of genetic deficit such as WS result in a brain that embodies a different organization from the TD brain. Consequently, qualitatively different learning mechanisms unfold over the course of development, resulting in qualitatively different knowledge representations.

I acknowledge that in studying developmental disorders, it is extremely important to understand the cognitive ability of interest as it unfolds over time. This may reveal crucial

aspects of the representation that would not be apparent by studying solely mature adults or cases of adults with brain damage. For example, by studying TD four- and six-year-olds in the present work, I find that although 2D boundary information is not the primary form of input for the reorientation mechanism, by the time children are six years of age, they are able to reorient by this abstract suggestion of a boundary. I also find several points of evidence that speak against the claim that general mechanisms of visual processing and navigation are radically different in WS. First, in behavior, we see that WS individuals reorient geometrically in the full Wall condition, matching the performance of TD children and adults. Second, the neural response of several control ROIs (FFA, LOC, and V1) did not differ between WS and CA controls. Even in the scene-selective regions of PPA, RSC, and TOS, the response to the Wall condition did not differ between WS and CA controls. Lastly, analysis of anterior/posterior subdivisions of the PPA hints that the functional organization of this region may follow the overall pattern shown in CA controls, albeit with specific reduced sensitivity to vertical boundary structure. In interpreting the findings of this thesis work, I prescribe to the view espoused by many others: that there are core systems of human knowledge (such as object, space, number, and social understanding) which emerge very early in life, under strong experiential constraints that limit both cognitive and neural architecture (Landau & Hoffman, 2012; Spelke, 2000; Carey, 2009). From this perspective, developmental impairments illustrate instances of malfunction that reflect the constraints imposed by this architecture.

Given this theoretical framework, the findings of this thesis research present a selective deficit to sensitivity to subtle variations in 3D boundary structure that is impaired as a result of the WS genetic deletion. Our previous research suggests that the spontaneous

analysis of surface layout geometry (Gallistel, 1990; Wang & Spelke, 2002) may not be entirely erased in WS. Rather, it appears that the ability is intact, yet fragile, for many members of the population (Ferrara & Landau, under review). The present research further addresses the nature of this fragility by demonstrating that the minimal 3D structure of the curb boundary is not sufficient to trigger geometric reorientation amongst members of this population. These results show that the WS geometric impairment is characterized by a reduced sensitivity to geometric structure, requiring especially salient presentation of geometry if it is to be used to accomplish reorientation. This reflects a fundamental absence of sensitivity to minimal boundary structure, which emerges early in TD children (Lee & Spelke, 2008; 2011).

In this thesis I couple behavioral and neuroimaging methods to test the hypothesis that unique encoding of different types of environmental boundaries in scene-selective cortices relates to their flexible use in reorientation. This hypothesis is supported by the unique case of WS; the inability to geometrically reorient by a slight curb boundary corresponds with an underlying lack of sensitivity to slight vertical boundary structure at the neural level. This suggests that if scene-selective areas are unable to encode crucial differences in different types of boundary cues (i.e., varying degrees of vertical structure), the ability to use these cues in navigation suffers as a result. Further research using additional methods (e.g., DTI) will help to further elucidate the links between scene representation in the brain and how this information informs navigation. Future studies with other populations that also show spatial impairments (e.g., Kabuki syndrome) will provide additional test cases for this hypothesis. Collectively, the findings of this thesis shed light on not only the WS

spatial deficit, but also provide insight to connections in healthy individuals between the bases of scene representation at the neural level and fluid navigation at the behavioral level.

APPENDIX A: MVPA ANALYSES FOR ADDITIONAL ROIS

To quantify whether the multivoxel patterns of TOS, LOC, FFA and V1 fit with one of the hypothetical models of interest (Distinctions between all Boundaries, Similarity between Mat and Curb, Similarity between Curb and Wall, or Similarity between Mat and Wall), we computed correlations between the data obtained for the confusion matrix of each ROI (generated by the SVM classifier) and each of the hypothetical models (the same method followed for PPA and RSC). These findings are described below.

Significant correlations were found between TOS in CA controls (Figure A.1.A) and the model for Distinctions between all Boundaries, $r = .94$, $p < .001$, as well as the model for Similarity between Mat and Curb, $r = .89$, $p = .001$. WS TOS (Figure A.1.A) showed significant correlations to these two models as well, $r = .88$, $p = .001$ and $r = .95$, $p < .001$, respectively. Correlations for the two remaining models were not significant for both groups (all ps > .29). A 2 × 2 mixed ANOVA for Group (WS, CA) and Model (Distinction between all Boundaries, Similarity between Mat and Curb) yielded a non-significant main effect of Model, $F(1,18) = 1.76$, $p = .20$, $\eta_p^2 = .09$. The main effect of Group was not significant, $F(1,18) = 0.07$, $p = .80$, $\eta_p^2 = .004$, nor was the Model by Group interaction, $F(1,18) = 0.52$, $p = .48$, $\eta_p^2 = .03$. Planned comparison t tests did not reveal significant differences between the two models for either the CA or WS group (CA: Cohen's $d = –0.10$, two-tailed $t(8) = –0.95$, $p = .93$, WS: Cohen's $d = –0.50$, two-tailed $t(8) = –1.46$, $p = .20$) (Figure A.1.B). Thus, it appears that this area, although scene-selective, does not share the same representational structure as either the PPA or RSC for boundaries. These results also indicate that the TOS of WS individuals may not differ from CA controls, although additional data are needed to support this conclusion.

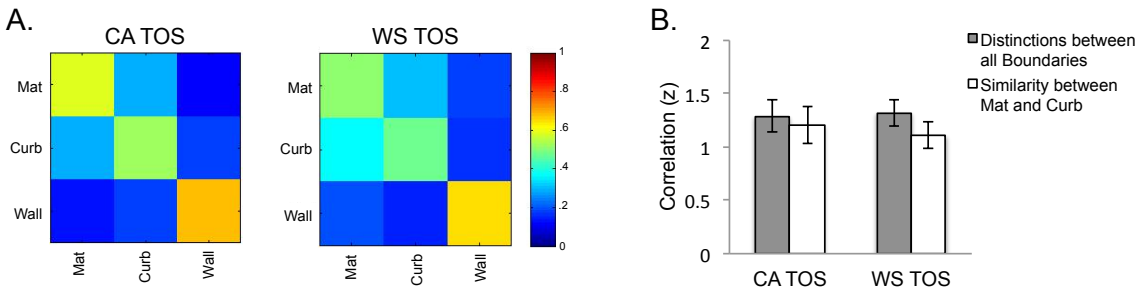

Figure A.1: A) Confusion matrices generated by the classifier when trained separately on neural patterns obtained from TOS of CA controls and TOS of WS participants. B) For both CA and WS groups, TOS does not show a higher correlation to either model. Error bars indicate +/– standard error of the mean.

For LOC (Figure A.2), none of the correlations to any of the four models were significant for either CA controls or the WS participants (all *p*s > .10). This finding is not surprising, given that LOC is an area that is selectively responsive to objects and not scenes.

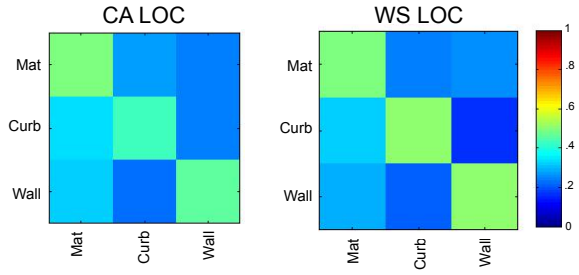

Figure A.2: Confusion matrices generated by the classifier when trained separately on neural patterns obtained from LOC of CA controls and LOC of WS participants.

For FFA (Figure A.3), none of the correlations to any of the four models were significant for either CA controls or the WS participants (all *p*s > .14). Again, this result of non-significance is in keeping with this ROI's selective sensitivity to specific content (faces) that differs from scenes.

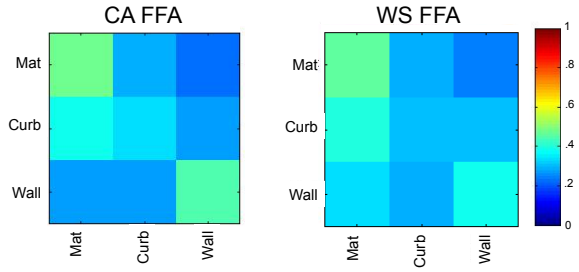

Figure A.3: Confusion matrices generated by the classifier when trained separately on neural patterns obtained from the FFA of CA controls and the FFA of WS participants.

We found a significant correlation between V1 of CA controls (Figure A.4.A) and the model that represents Distinctions between all Boundaries, $r = .98$, $p < .001$. The correlation to the model for Similarity between Mat and Curb was also significant, $r = .81$, $p = .003$. WS V1 (Figure A.4.A) also showed significant correlations to these same two models, $r = .95$, $p < .001$ and $r = .78$, $p = .02$, respectively. Correlations for the two remaining models were not significant for both groups (all ps > .09). The 2 × 2 mixed ANOVA yielded a significant main effect of Model, $F(1,19) = 19.69$, $p < .001$, $\eta_p^2 = .51$. The main effect of Group was not significant, $F(1,19) = 2.12$, $p = .16$, $\eta_p^2 = .10$, and the Model by Group interaction was not significant, $F(1,19) = 3.72$, $p = .08$, $\eta_p^2 = .17$. Planned comparison t tests revealed that V1 of both CA controls and WS participants had a significantly higher correlation to the model for Distinction between all Boundaries over the model for Similarity between Mat and Curb (CA: Cohen's $d = 3.67$, two-tailed $t(7) = 6.54$, $p < .001$, WS: Cohen's $d = 1.76$, two-tailed $t(7) = 2.53$, $p = .04$) (Figure A.4.B). As was discussed for analyses of the univariate response of V1, this ROI's sensitivity to the differences in vertical height between all three boundary conditions is driven by differences in the low-level visual properties of the stimulus images. Because the main effect of Group and the Group by Model interaction were not significant,

these results provide further evidence that early visual processing in WS does not differ from CA controls.

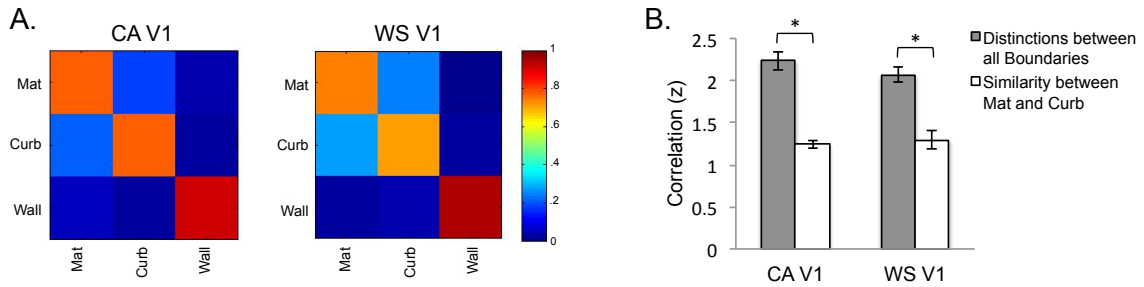

Figure A.4: A) Confusion matrices generated by the classifier when trained separately on the neural patterns obtained from V1 of CA controls and V1 of WS participants. B) For both CA and WS groups, V1 shows a higher correlation to the model for Distinctions between all Boundaries. Error bars indicate +/– standard error of the mean. Asterisks indicate a significant difference between the two models, $p < .05$.

BIBLIOGRAPHY

Aggleton, J. P., & Vann, S. D. (2004). Testing the importance of the retrosplenial navigation system: lesion size but not strain matters: a reply to Harker and Whishaw. *Neuroscience & Biobehavioral Reviews, 28*, 525–531.

Aguirre, G. K., & D'Esposito, M. (1999). Topographical disorientation: a synthesis and taxonomy. *Brain, 122*, 1613–1628.

Aguirre, G. K., Detre, J. A., Alsop, D. C., & D'Esposito, M. (1996). The parahippocampus subserves topographical learning in man. *Cerebral Cortex, 6,* 823–829.

Aguirre, G. K., Zarahn, E., & D'Esposito, M. (1998). An area within human ventral cortex sensitive to ''building'' stimuli: evidence and implications. *Neuron, 21*, 373–383.

Alsaadi, T., Binder, J. R., Lazar, R. M., Doorani, T., & Mohr, J. P. (2000). Pure topographic disorientation: a distinctive syndrome with varied localization. *Neurology, 54,* 1864–1866.

Alvarado, M. C., & Bachevalier, J. (2000). Revisiting the maturation of medial temporal lobe memory functions in primates. *Learning & Memory, 7,* 244–256.

American Academy of Pediatrics. (2001). Health care supervision for children with Williams syndrome. *Pediatrics, 107*, 1192–1204.

Akers, K. G., Candelaria, F. T., & Hamilton, D. A. (2007). Preweaning rats solve the Morris water task via directional navigation. *Behavioral Neuroscience, 12*, 1426–1430.

Arcaro, M. J., McMains, S., Singer, B., & Kastner, S. (2009). Retinotopic organization of human ventral visual cortex. *Journal of Neuroscience, 29,* 10638–10652.

Atkinson, J., Anker, S., Braddick, O., Nokes, L., Mason, A., & Braddick, F. (2002). Visual and visuospatial development in young children with Williams syndrome. *Developmental Medicine & Child Neurology, 43*, 330–337.

Baldassano, C., Beck, D. M., & Fei-Fei, L. (2013). Differential connectivity within the parahippocampal place area. *NeuroImage, 75,* 228–237.

Bar, M., & Aminoff, E. (2003). Cortical analysis of visual context. *Neuron, 38,* 347–358.

Barrash, J., Damasio, H., Adolphs, R., & Tranel, D. (2000). The neuroanatomical correlates of route learning impairment. *Neuropsychologia, 38*, 820–836.

Barry, C., Lever, C., Hayman, R., Hartley, T., Burton, S., O'Keefe, J., Jeffery, K., & Burgess, N. (2006). The boundary vector cell model of place cell firing and spatial memory. *Annual Review of Neuroscience, 17*, 71–97.

Bennett, A. T. D. (1996). Do animals have cognitive maps? *Journal of Experimental Biology, 199*, 219–224.

Bird, C. M., Cappont, C., King, J. A., Doeller, C. F., & Burgess, N. (2010). Establishing the boundaries: the hippocampal contribution to imagining scenes. *Journal of Neuroscience, 30*(35), 11688–11695.

Bird, C. M., Vargha-Khadem, F., & Burgess, N. (2008). Impaired memory for scenes but not faces in developmental hippocampal amnesia: a case study. *Neuropsychologia, 46*, 1050– 1059.

Bohbot, V. D., Iaria, G., & Petrides, M. (2004). Hippocampal function and spatial memory: evidence from functional neuroimaging in healthy participants and performance of patients with medial temporal lobe resections. *Neuropsychology, 18*, 418–425.

Bohbot, V. D., Lerch, J., Thorndycraft, B., Iaria, G., & Zijdenbos, A. P. (2007). Gray matter differences correlate with spontaneous strategies in a human virtual navigation task. *Journal of Neuroscience, 27*, 10078–10083.

Bures, J., Fenton, A. A., Kaminsky, Y., & Zinyuk, L. (1997). Place cells and place navigation. *Proceedings of the National Academy of Sciences (USA), 94*(1), 343–350.

Burgess, N. (2008). Spatial cognition and the brain. *Annals of the New York Academy of Sciences, 1124*, 77–97.

Burgess, N., Jackson, A., Hartley, T., & O'Keefe, J. (2000). Predictions derived from modeling the hippocampal role in navigation. *Biological Cybernetics, 83,* 301–312.

Burgess, N., Jeffery, K. J., & O'Keefe, J. (1999). The hippocampal and parietal foundations of spatial cognition. Oxford: Oxford University Press.

Burgess, N., Maguire, E. A., & O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron, 35*, 625–641.

Bush, D., Barry, C., & Burgess, N. (2014). What do grid cells contribute to place cell firing? *Trends in Neurosciences, 37*, 136–145.

Carey, S. (2009). *The origin of concepts.* Oxford University Press, USA.

Caspers, S., Eickhoff, S. B., Rick, T., Von Kapri, A., Kuhlen, T., Huang, R., Shah, N. J., & Zilles, K. (2011). Probabilistic fibre tract analysis of cytoarchitectonically defined human inferior parietal lobule areas reveals similarities to macaques. *Neuroimage, 58,* 362–380.

Chapman, C. A., du Plessis, A., & Pober, B. R. (1996). Neurologic findings in children and adults with Williams syndrome. *Journal of Child Neurology, 11*, 63–65.

Cheng, K. (1986). A purely geometric module in the rats' spatial representation. *Cognition, 23,* 149–178.

Cheng, K. (2008). Whither geometry? troubles of the geometric module. *Trends in Cognitive Sciences, 12*(9), 355–361.

Cheng, K., & Gallistel, C. R. (1984). Testing the geometric power of an animal's spatial representation. In H. L. Roitblat, T. G. Bever, & H. S. Terrace (Eds.), Animal cognition: Proceedings of the Harry Frank Guggenheim conference. Hillsdale, NJ: Erlbaum.

Cheng, K., & Newcombe, N. S. (2005). Is there a geometric module for spatial orientation? Squaring theory and evidence. *Psychonomic Bulletin & Review, 12*, 1–23.

Chiandetti, C., & Vallortigara, G. (2008). Is there an innate geometric module? effects of experience with angular geometric cues on spatial re-orientation based on the shape of the environment. *Animal Cognition, 11,* 139–146.

de Almeida, L., Idlart, M., & Lisman, J. E. (2009). The input-output transformation of the hippocampal granule cells: from grid cells to place fields. *Journal of Neuroscience, 29*, 7504–7512.

Dilks, D., Hoffman, J. E., & Landau, B. (2008). Vision for perception and vision for action: normal and unusual development. *Developmental Science, 11*(4), 474–486.

Dilks, D. D., Julian, J. B., Paunov, A. M., & Kanwisher, N. (2013). The occipital place area is causally and selectively involved in scene perception. *Journal of Neuroscience, 33*(4), 1331–1336.

Dilks, D. D., Julian, J. B., Kubilius, J., Spelke, E. S., & Kanwisher, N. (2011). Mirror-image sensitivity and invariance in object and scene processing pathways. *Journal of Neuroscience, 31*, 11305–11312.

Dillon, M. R., Huang, Y., & Spelke, S. (2013). Core foundations of abstract geometry. *Proceedings of the National Academy of Sciences (USA)*, *110*(35), 14191–14195.

Doeller, C. F., & Burgess, N. (2008). Distinct error-correcting and incidental learning of location relative to landmarks and boundaries. *Proceedings of the National Academy of Sciences (USA), 105,* 5909–5914.

Doeller, C. F., King J. A., & Burgess, N. (2008). Parallel striatal and hippocampal systems for landmarks and boundaries in spatial memory. *Proceedings of the National Academy of Sciences (USA), 105,* 5915–5920.

Eckert, M. A., Hu, D., Eliez, S., Bellugi, U., Galaburda, A., Korenberg, J., Mills, D., & Reiss, A. L. (2005). Evidence for superior parietal impairment in Williams syndrome.

Neurology, 64, 152–153.

Ekstrom, A. D., Kahana, M. J., Caplan, J. B., Fields, T. A., Isham, E. A., Newman, E. L., & Fried, I. (2003). Cellular networks underlying human spatial navigation. *Nature, 425,* 184–188.

Elliott, C. D. (1990). *Differential Abilities Scales*. San Antonio, TX: Psychological Corporation.

Epstein, R. A. (2008). Parahippocampal and retrosplenial contributions to human spatial navigation. *Trends in Cognitive Sciences, 12,* 388–396.

Epstein, R. A., Graham, K. S., & Downing, P. E. (2003). Viewpoint-specific scene representations in human parahippocampal cortex. *Neuron, 37*, 865–876.

Epstein, R., Harris, A., Stanley, D., & Kanwisher, N. (1999). The parahippocampal place area: recognition, navigation, or encoding? *Neuron, 23*, 115–125.

Epstein, R. A., Higgins, S. J., Jablonski, K., & Feiler., A. M. (2007a). Visual scene processing in familiar and unfamiliar environments. *Journal of Neurophysiology, 97*, 3670–3683.

Epstein, R., & Kanwisher, N. (1998). A cortical representation of the local visual environment. *Nature, 392*, 598–601.

Epstein, R. A., Parker, W. E., & Feiler, A. M. (2007b). Where am I now? distinct roles for parahippocampal and retrosplenial cortices in place recognition. *Journal of Neuroscience, 27*, 6141–6149.

Fairhall, S. L., & Caramazza, A. (2013). Category selective neural substrates for person- and place-related concepts. *Cortex, 49*(10), 2748–2757.

Fanselow, M. S., & Dong, H. (2010). Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron, 65*(1), 7–19.

Farran, E. K., Blades, M., Boucher, J., & Tranter, L. J. (2010). How do individuals with Williams syndrome learn a route in a real‐world environment? *Developmental Science, 13*(3), 454–468.

Farran, E. K., Courbois, Y., Van Herwegen, J., & Blades, M. (2012). How useful are landmarks when learning a route in a virtual environment? evidence from typical development and Williams syndrome. *Journal of Experimental Child Psychology, 111*, 571–586.

Ferrara, K., & Landau, B. (2013). Reorientation and spatial language: evidence from Williams syndrome and typically developing children. Talk presented at the Society

of Research in Child Development Biennial meeting, Seattle, WA.

Ferrara, K., & Landau, B. (under review). Geometric and featural systems, separable and combined: Evidence from reorientation in people with Williams syndrome.

Ferrara, K., & Park, S. (2014). *Neural representation of different boundary cues*. Talk presented at the annual meeting of the Society for Neuroscience, Washington, DC.

Fodor, J. (1983). *The modularity of the mind: an essay on faculty psychology*. Cambridge, MA: MIT Press.

Foo, P., Warren, W. H., Duchon, A., & Tarr, M. J. (2005). Do humans integrate routes into a cognitive map? map- versus landmark-based navigation of novel shortcuts. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 31,* 195–215.

Furman, A. J., Clements-Stephens, A. M., Marchette, S. A., & Shelton, A. L. (2014). Persistent and stable biases in spatial learning mechanisms predict navigational style. *Cognitive, Affective, & Behavioral Neuroscience, 14*, 1375–1391.

Fyhn, M., Molden, S., Witter, M. P., Moser, E. I., & Moser, M.-B. (2004). Spatial representation in the entorhinal cortex. *Science, 305,* 1258–1264.

Gallistel, C. R. (1990). *The organization of learning*. Cambridge, MA: MIT Press.

Gallistel, C. R., & Matzel, L. D. (2013). The neuroscience of learning: beyond the hebbian space. *Annual Review of Psychology, 64,* 169–200.

Gaser, C., Luders, E., Thompson, P. M., Lee, A. D., Dutton, R. A., Geaga, J. A., Hayashi, K. M., Bellugi, U., Galaburda, A. M., & Korenberg, J. R. (2006). Increased local gyrification mapped in Williams syndrome. *NeuroImage, 33*(1), 46–54.

Ghaem, O., Mellet, E., Crivello, F., Tzourio, N., Mazoyer, B., Berthoz, A., & Denis, M. (1997). Mental navigation along memorized routes activates the hippocampus, precuneus, and insula. *Neuroreport, 8*, 739–744.

Gogtay N., Nugent T. F., Herman, D. H., Ordonez, A., Greenstein, D., Hayashi, K. M. Clasen, L., Toga, A. W., Giedd, J. N., Rapoport, J. L., & Thompson, P. M. (2006). Dynamic mapping of normal human hippocampal development. *Hippocampus, 16*, 664–672.

Golarai, G., Ghahremani, D. G., Whitfield-Gabrieli, S., Reiss A, Eberhardt, J. L., & Gabrieli, J. D. (2007). Differential development of high-level visual cortex correlates with category-specific recognition memory. *Nature Neuroscience, 10*, 512–522.

Gouteux, S., & Spelke, E. S. (2001). Children's use of geometry and landmarks to reorient in

an open space. *Cognition, 81,* 119–148.

Gouteux, S., Thinus-Blanc, C., & Vauclair, J. (2001). Rhesus monkeys use geometric and non-geometric information during a reorientation task. *Journal of Experimental Psychology: General, 130*, 505–519.

Gray, E. R., Bloomfield, L. L., Ferrey, A., Spetch, M. L., & Sturdy, C. B. (2005). Spatial encoding in mountain chickadees: features overshadow geometry. *Biology Letters, 1,* 314–317.

Greene, K. K., Donders, J., & Thoits, T. (2006). Topographical heading disorientation: a case study. *Applied Neuropsychology, 13*, 269–274.

Grill-Spector, K. (2003). The neural basis of object perception. *Current Opinion in Neurobiology, 13,* 159–166.

Grill-Spector, K., Kourtzi, Z., & Kanwisher, N. (2001). The lateral occipital complex and its role in object recognition. *Vision Research, 41,* 1409–1422.

Hafting, T. Fyhn, M., Molden, S., Moser, M. B., & Moser, E. I. (2005). Microstructure of a spatial map in the entorhinal cortex. *Nature, 436*, 801–806.

Hamilton, D. A., Akers, K. G., Johnson, T. E., Rice J. P., Candelaria, F. T., Sutherland R. J., Weisend, M. P., & Redhead, E. S. (2008). The relative influence of place and direction in the Morris water task. *Journal of Experimental Psychology: Animal Behavior Processes, 34*, 31–53.

Hamilton, D. A., Akers, K. G., Weisend, M. P., & Sutherland, R. J. (2007). How do room and apparatus cues control navigation in the Morris water task? evidence for distinct contributions to a movement vector. *Journal of Experimental Psychology: Animal Behavior Processes, 33,* 100–114.

Hamilton, D. A., Johnson, T. E., Redhead, E. S., & Verney, S. P. (2009). Control of human and rodent navigation by room and apparatus cues. *Behavioural Processes, 81,*154–169.

Harel, A., Kravitz, D. J., & Baker, C. I. (2013). Deconstructing visual scenes in cortex: gradients of object and spatial layout information. *Cerebral Cortex, 23*, 947–957.

Hartley, T., Burgess, N., Lever, C., Cacucci, F., & O'Keefe, J. (2000). Modeling place fields in terms of the cortical inputs to the hippocampus. *Hippocampus, 10,* 369–379.

Hartley, T., Maguire, E. A., Spiers, H. J., & Burgess, N. (2003). The well-worn route and the path less traveled: distinct neural bases of route following and wayfinding in humans. *Neuron, 37*, 877–888.

Hasselmo, M. E. (2009). A model of episodic memory: mental time travel along encoded trajectories using grid cells. *Neurobiology of Learning and Memory, 92*, 559–573.

Hasson, U., Harel, M., Levy, I., & Malach, R. (2003). Large-scale mirror-symmetry organization of human occipito-temporal object areas. *Neuron, 37*, 1027–1041.

Hayman, R. M., & Jeffery, K. J. (2008). How heterogenous place cell responding arises from homogenous grids: a contextual gating hypothesis. *Hippocampus, 18*, 1301–1313.

Hayward, A., McGregor, A., Good, M. A., & Pearce, J. M. (2003). Absence of overshadowing and blocking between landmarks and the geometric cues provided by the shape of a test arena. *Quarterly Journal of Experimental Psychology, 56*, 114–126.

Hermer, L., & Spelke, E. (1994). A geometric process for spatial reorientation in young children. *Nature*, *370*, 57–59.

Hermer, L., & Spelke, E. (1996). Modularity and development: the case of spatial reorientation. *Cognition, 61*, 195–232.

Holdstock, J. S., Mayes, A. R., Cezayirli, E., Isaac, C. L., Aggleton, J. P., & Roberts, N. (2000). A comparison of egocentric and allocentric memory in a patient with selective hippocampal damage. *Neuropsychologia, 38*, 410–425.

Huttenlocher, J., Lourenco, S. F., & Vasilyeva, M. (2006). Perspectives on spatial development. In L. B. Smith, M. Gasser, & K. Mix (Eds.). *The spatial foundations of cognition and language.* New York, NY: Oxford University Press.

Huttenlocher J., & Vasilyeva, M. (2003). How toddlers represent enclosed spaces. *Cognitive Science, 27*(5), 749–766.

Iaria, G., Petrides, M., Dagher, A., Pike, B., & Bohbot, V. (2003). Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: variability and change with practice. *Journal of Neuroscience, 23,* 5945–5952.

Incisa della Rocchetta, A., Samson, S., Ehrle, N., Denos, M., Hasboun, D., & Baulac, M. (2004). Memory for visuospatial location following selective hippocampal sclerosis: use of different coordinate systems. *Neuropsychology, 18*, 15–28.

Ino, T., Doi, T., Hirose, S., Kimura, T., Ito, J., & Fukuyama, H. (2007). Directional disorientation following left retrosplenial hemorrhage: a case report with fMRI studies. *Cortex, 43*, 248–254.

Ino T., Inoue, Y., Kage, M., Hirose, S., Kimura, T., & Fukuyama, H. (2002). Mental navigation in humans is processed in the anterior bank of the parieto-occipital sulcus. *Neuroscience Letters, 322*, 182–186.

Jackowski, A. P., & Schultz, R. T. (2005). Foreshortened dorsal extension of the central sulcus in Williams syndrome. *Cortex, 41*(3), 282–290.

Janzen, G., & van Turennout M. (2004). Selective neural representation of objects relevant for navigation. *Nature Neuroscience, 7*(6), 673–677.

Jernigan, T. L., & Bellugi, U. (1990). Anomalous brain morphology on magnetic resonance images in Williams syndrome and Down syndrome. *Archives of Neurology, 47*, 529–533.

Johnson, M. R., Mitchell, K. J., Raye, C. L., D'Esposito, M., & Johnson, M. K. (2007). A brief thought can modulate activity in extrastriate visual areas: top-down effects of refreshing just-seen visual stimuli. *NeuroImage, 37*, 290–299.

Johnstone, T., Ores Walsh, K. S., Greischar, L. L., Alexander A. L., Fox, A. S., Davidson, R. J., & Oakes, T. R. (2006). Motion correction and the use of motion covariates in multiple-subject fMRI analysis. *Human Brain Mapping, 27*(10), 779–788.

Kahn, I., Andrews-Hanna, J. R., Vincent, J. L., Snyder, A. Z., & Buckner, R. L. (2008). Distinct cortical anatomy linked to subregions of the medial temporal lobe revealed by intrinsic functional connectivity. *Journal of Neurophysiology, 100*, 129–139.

Kanwisher, N., McDermott, J., & Chun, M. M. (1997) The fusiform face area: a module in human extrastriate cortex specialized for face perception. *Journal of Neuroscience, 17*, 4302–4311.

Karmiloff-Smith, A. (1998). Development itself is the key to understanding developmental disorders. *Trends in Cognitive Sciences, 2*, 389–398.

Karmiloff-Smith, A. (2007). Atypical epigenesis. *Developmental Science, 10*(1), 84.

Katayama, K., Takahashi, N., Ogawara, K., & Hattori, T. (1999). Pure topographical disorientation due to right posterior cingulate lesion. *Cortex, 35*, 279–282.

Kaufman, A. S., & Kaufman, N. L. (2004). *Kaufman Brief Intelligence Test*. 2nd ed. Circle Pines, MN: American Guidance Service.

Kelly, D. M., Spetch, M. L., & Heath, C. D. (1998). Pigeons' (Columba livia) encoding of geometric and featural properties of a spatial environment. *Journal of Comparitive Psychology, 112*, 259–269.

Kim, D. S., & Kim, M. (2005). Combining functional and diffusion tensor MRI. *Annals of the New York Academy of Sciences, 1064*, 1–15.

King, J. A., Burgess, N., Hartley, T., Vargh-Khadem, K., & O'Keefe, J. (2002). Human hippocampus and viewpoint dependence in spatial memory. *Hippocampus, 12*, 811–

820.

Kippenhan, J. S., Olsen, R. K., Mervis, C. B., et al. (2005). Genetic contributions to human gyrification: sulcal morphometry in Williams syndrome. *Journal of Neuroscience, 25*, 7840–7846.

Klatzky, R. L. (1998). Allocentric and egocentric spatial representations: definition, distinctions, and interconnections. In C. Freska, C. Habel, K. F. Wender, (Eds.), *Spatial cognition: an interdisciplinary approach to representing and processing spatial knowledge.* Berlin, Germany: Springer-Verlag.

Knierim, J. J., & Hamilton, D. A. (2011). Framing spatial cognition: neural representation of proximal and distal frames of reference and their roles in navigation. *Physiological Reviews, 91,* 1245–1279.

Kobayashi, Y., & Amaral, D. G. (2003). Macaque monkey retrosplenial cortex: II. cortical afferents. *Journal of Comparative Neurology, 466*, 48–79.

Kogure, D., Matsuda, H., Ohnishi, T., Asada, M. U., Kunihiro, T., Nakano, S., & Takashi, M. (2000). Longitudinal evaluation of early Alzheimer's disease using brain perfusion SPECT. *Journal of Nuclear Medicine, 41*, 1155–1162.

Konen, C. S., & Kastner, S. (2008). Two hierarchically organized neural systems for object information in human visual cortex. *Nature Neuroscience, 11*, 224–231.

Kosslyn, S. M., Pick, H. L., & Fariello, G. R. (1974). Cognitive maps in children and men. *Child Development, 45,* 707–716.

Koster-Hale, J., Saxe, R., Dungan, J., & Young, L. L. (2013). Decoding moral judgments from neural representations of intentions. *Proceedings of the National Academy of Sciences (USA),110,* 5648–5653.

Kourtzi, Z., & Kanwisher, N. (2001). Representation of perceived object shape by the human lateral occipital complex. *Science, 293,* 1506–1509.

Kravitz, D. J., Kriegeskorte, N., & Baker, C. I. (2010). High-level visual object representations are constrained by position. *Cerebral Cortex, 20*, 2916–2925.

Kravitz, D. J., Peng, C. S., & Baker, C. I. (2011a). Real-world scene representations in high-level visual cortex – it's the spaces not the places. *Journal of Neuroscience, 31*, 7322– 7333.

Kravitz, D. J., Saleem, K. S., Baker, C. I., & Mishkin, M. A. (2011b). A new neural framework for visuospatial processing. *Nature Reviews Neuroscience, 12*, 217–230.

Kravitz, D. J. Saleem, K. S., Baker, C. I., Ungerleider, L. G., & Mishkin, M. (2013). The ventral visual pathway: an expanded neural framework for the processing of object

quality. *Trends in Cognitive Sciences, 17*(1), 26–49.

Lakusta, L., Dessalegn, B., & Landau, B. (2010). Impaired geometric reorientation caused by genetic defect. *Proceedings of the National Academy of Sciences (USA), 107,* 2813–2817.

Landau, B., & Hoffman, J. E. (2012). *Spatial representation: from gene to mind*. New York, NY: Oxford University Press.

Landau, B., Hoffman, J., & Kurz, N. (2006). Object recognition with severe spatial deficits in Williams syndrome: sparing and breakdown. *Cognition, 100*(3), 483–510.

Larsson, J., & Heeger, D. J. (2006). Two retinotopic visual areas in human lateral occipital cortex. *Journal of Neuroscience, 26*, 13128–13142.

Learmonth, A., Newcombe, N.S., & Huttenlocher, J. (2001). Toddler's use of metric information and landmarks to reorient. *Journal of Experimental Child Psychology, 80*, 225–244.

Lee, S. A., Sovrano, V. A., & Spelke, E. S. (2012). Navigation as a source of geometric knowledge: young children's use of length, angle, distance, and direction in a reorientation task. *Cognition, 123*, 144–161.

Lee, S. A., & Spelke, E. (2008). Children's use of geometry for navigation. *Developmental Science, 11*(5), 743–749.

Lee, S. A., & Spelke, E. (2010). A modular geometric mechanism for reorientation in children. *Cognitive Psychology, 61*, 152–176.

Lee, S. A., & Spelke, E. (2011). Young children reorient by computing layout geometry, not by matching images of the environment. *Psychonomic Bulletin & Review, 18*, 192–198.

Lever, C., Wills, T., Cacucci, F., Burgess, N., & O'Keefe, J. (2002). Long-term plasticity in hippocampal place-cell representation of environmental geometry. *Nature, 416,* 90–94.

Lever, C., Burton, S., Ali Jeewajee, A., O'Keefe, J., & Burgess, N. (2009). Boundary vector cells in the subiculum of the hippocampal formation. *Journal of Neuroscience, 29,* 9771–77.

Lew, A. R., Foster, K. A., & Bremner, J. G. (2006). Disorientation inhibits landmark use in 12–18-month-old infants. *Infant Behavior and Development, 29*, 334–341.

Libby, L. A., Ekstrom, A. D., Ragland, J. D., & Ranganath, C., (2012). Differential connectivity of perirhinal and parahippocampal cortices within human hippocampal subregions revealed by high-resolution functional imaging. *Journal of Neuroscience,*

32, 6550–6560.

Lourenco, S. F., & Huttenlocher, J. (2007, April). Coding location in enclosed spaces: is geometry the principle? Paper presented at the biennial meeting of the Society for Research in Child Development, Boston, MA.

Lynch, M. A. (2004). Long-term potentiation and memory. *Physiological Reviews, 84*, 87–136.

MacDonald, S. E., Spetch, M. L., Kelly, D. M., & Cheng, K. (2004). Strategies in landmark use by children, adults, and marmoset monkeys. *Learning and Motivation, 35*(4), 322–347.

MacEvoy, S. P., & Epstein, R. A. (2007). Position selectivity in scene- and object-responsive occipitotemporal regions. *Journal of Neurophysiology, 98*, 2089–2098.

Maguire, E. A., Burgess, N., Donnett, J. G., Frackowiak, R. S. J., Frith, C. D., & O'Keefe, J. (1998). Knowing where and getting there: a human navigation network. *Science, 280*, 921–924.

Maguire, E. A., Frackowiak, R. S. J., & Frith, C. D. (1997). Recalling routes around London: activation of the right hippocampus in taxi drivers. *Journal of Neuroscience, 17*, 7103– 7110.

Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S. J., & Firth, C. D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *Proceedings of the National Academy of Sciences (USA),* 97, 4398–4403

Maguire, E. A., Nannery, R., & Spiers, H. J. (2006). Navigation around London by a taxi driver with bilateral hippocampal lesions. *Brain, 129*, 2894–2907.

Malach, R., Reppas, J. B., Benson, R. R., Kwong, K. K., Jiang, H., Kennedy, W. A., Ledden, P. J., Brady, T. J., Rosen, B. R., & Tootell, R. B. (1995). Object-related activity revealed by functional magnetic resonance imaging in human occipital cortex. *Proceedings of the National Academy of Sciences (USA), 92,* 8135–8139.

Marchette, S. A., Vass, L. K., Ryan, J., & Epstein, R. A. (2014). Anchoring the neural compass: coding of local spatial reference frames in human medial parietal lobe. *Nature Neuroscience, 17,* 1598–1606.

Marenco, S., Siuta, M. A., Kippenhan, J. S., Grodofsky, S., Chang, W., Kohn, P., Mervis, C. B., Morris, C. A., Weinberger, D. R., & Meyer-Lindenberg, A. (2007). Genetic contributions to white matter architecture revealed by diffusion tensor imaging in Williams syndrome. *Proceedings of the National Academy of Sciences (USA), 104*(38), 15117.

McGauran, A. M. T., Harvey, D., Cunningham, L., Craig, S., & Commins, S. (2004). Retention of cue based associations in the water maze is time-dependent and sensitive to disruption by rotating the starting position. *Behavioral Brain Research, 151*, 255–266.

Mendez, M. F., & Cherrier, M. M. (2003). Agnosia for scenes in topographagnosia. *Neuropsychologia, 41,* 1387–1395.

Mercuri, E., Atkinson, J., Braddick, O., Rutherford, M. A., Cowan, F. M., Counsell, S. J. et al. (1997). Chiari I malformation in asymptomatic young children with Williams syndrome: clinical and MRI study. *European Journal of Pediatric Neurology, 1*, 177–181.

Mervis, C. B., Robinson, B. F., Bertrand, J., Morris, C. A., Klein-Tasman, B. P., & Armstrong, S. C. (2000). The Williams syndrome cognitive profile. *Brain and Cognition, 44*, 604–628.

Meyer-Lindenberg, A., Kohn, P., Mervis, C. B., Kippenhan, J. S., Olsen, R. K., Morris, C. A., & Berman, K. F. (2004). Neural basis of genetically determined visuospatial construction deficit in Williams syndrome. *Neuron, 43*(5), 623–631.

Meyer-Lindenberg, A., Mervis, C. B., & Berman, K. F. (2006). Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behaviour. *Nature Reviews Neuroscience, 7*(5), 380–393.

Meyer-Lindenberg, A., Mervis, C. B., Sarpal, D., Koch, P., Steele, S., Kohn, P., Marenco, S., Morris, C. A., Das, S., & Kippenhan, S. (2005). Functional, structural, and metabolic abnormalities of the hippocampal formation in Williams syndrome. *Journal of Clinical Investigation, 115*(7), 1888–1895.

Milner, A. D., & Goodale, M. A. (2008). Two visual systems re-viewed. *Neuropsychologia, 46*(3), 774–785.

Morris, C. A. (2006a). The dysmorphology, genetics, and natural history of Williams-Beuren syndrome. In C. A. Morris, H. Lenhoff, P. Wang (Eds.), *Williams-Beuren syndrome: Research, evaluation, and treatment.* (pp. 3–17). Baltimore, MD: Johns Hopkins University Press.

Morris, C. A. (2006b). Genotype-phenotype correlations in Williams-Beuren syndrome. In C. A. Morris, H. Lenhoff & P. Wang (Eds.), *Williams-Beuren syndrome: Research, evaluation, and treatment* (pp. 59–82). Baltimore, MD: Johns Hopkins University Press.

Morris, R. G. M. (1981). Spatial localisation does not require the presence of local cues. *Learning Motivation, 12*, 239–260.

Moser, E. I., Kropff, E., & Moser, M-B. (2008). Place cells, grid cells, and the brain's spatial representation system. *Annual Review of Neuroscience, 31,* 69.

Moser, M. B., Moser, E. I., Forrest, E., Andersen, P., Morris, R. G. (1995). Spatial learning with a minislab in the dorsal hippocampus. *Proceedings of the National Academy of Sciences (USA), 92*, 9697–9701.

Mou, W., & Zhou, R. (2013). Defining a boundary in goal localization: infinite number of points or extended surfaces. *Journal of Experimental Psychology, 39*(4), 1115–1127.

Muller, R. (1996). A quarter of a century of place cells. *Neuron, 17*, 813–822.

Musolino, J., Chunyo, G., & Landau, B. (2010). Uncovering knowledge of core syntactic and semantic principles in individuals with Williams syndrome. *Language Learning and Development, 6*, 126–161.

Nakamura, K., Kawashima, R., Sato, N., Nakamura, A., Sugiura, M., Kato, T., Hatano, K., Ito, K., Fukuda, H., Schormann, T., & Ziles, K. (2000). Functional delineation of the human occipito-temporal areas related to face and scene processing: A PET study. *Brain, 123*, 1903–1912.

Nardini, M., Atkinson, J., Braddick, O., & Burgess, N. (2008). Developmental trajectories for spatial frames of reference in Williams syndrome. *Developmental Science, 11,* 583–595.

Newcombe, N. S. (2006). Evidence for and against a geometric module: the roles of language and action. In J. Reisser, J. Lockman, & C. Nelson (Eds.), *Action as an organizer of learning and development*. Minnesota Symposium on Child Development Series. Lawrence Earlbaum Associates, New Jersey.

Newcombe, N. S., & Huttenlocher, J. (2000). *Making space: The development of spatial representation and reasoning*. Cambridge, MA: MIT Press.

Newcombe, N. S., & Liben, L. S. (1982). Barrier effects in the cognitive maps of children and adults. *Journal of Experimental Child Psychology, 34*, 46–58.

O'Hearn, K., Roth, J. K., Courtney, S. M., Luna, B., Street, W. Terwillinger, R., & Landau, B. (2011). Object recognition in Wiliams syndrome: uneven ventral stream activation. *Developmental Science, 14*(3), 549–565.

O'Keefe, J., & Burgess, N. (2005). Dual phase and rate coding in hippocampal place cells: theoretical significance and relationship to entorhinal grid cells. *Hippocampus, 15*, 853–866.

O'Keefe, J., & Burgess, N. (1996). Geometric determinants of the place fields of hippocampal neurons. *Nature, 381*, 425–428.

O'Keefe, J., & Dostrovsky, J. (1971). The hippocampus as a spatial map. *Brain Research*, *34(*1), 171–175.

O'Keefe, J., & Nadel, L. (1978). *The Hippocampus as a cognitive map*. Oxford, UK: Clarendon Press.

Olsen, R. K., Kippenhan, J. S., Japee, S., Kohn, P., Mervis, C. B., Saad, Z. S., Morris, C. A., Meyer-Lindenberg, A., & Berman, K. F. (2009). Retinotopically defined primary visual cortex in Williams syndrome. *Brain, 132*(3), 635.

Orban, P., Rauchs, G., Balteau, E., Degueldre, C., Luxen, A., Maquet, P., & Peigneux, P. (2006). Sleep after spatial learning promotes covert reorganization of brain activity. *Proceedings of the National Academy of Sciences (USA), 103,* 7124–7129.

Osawa, A., Maeshima S., & Kunishio K. (2008). Topographic disorientation and amnesia due to cerebral hemorrhage in the left retrosplenial region. *European Neurology, 59*, 79–82.

Packard, M. G., & Knowlton, B. J. (2002). Learning and memory functions of the basal ganglia. *Annual Review of Neuroscience, 25*, 563–593.

Packard, M. G., & McGaugh, J. L. (1996). Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiolology of Learning and Memory, 65*, 65–72.

Palomares, M., Landau, B., & Egeth, H. (2009). Orientation perception in Williams syndrome: discrimination and integration. *Brain and Cognition, 70*(1), 21–30.

Park, S., Brady, T. F., Greene, M. R., & Oliva, A. (2011). Disentangling scene content form spatial boundary: complementary roles for the parahippocampal place area and lateral occipital complex in representing real-world scenes. *Journal of Neuroscience*, *31*(4), 1333–1340.

Park, S., & Chun, M. M. (2009). Different roles of the parahippocampal place area (PPA) and retrosplenial cortex (RSC) in panoramic scene perception. *Neuroimage, 47*, 1747–1756.

Park, S., Konkle, T., & Oliva, A. (2015). Parametric coding of the size and clutter of natural scenes in the human brain. *Cerebral Cortex, 25*(7), 1792–1805.

Park, S., Levine, M., & Dunne, M. (2013). Neural representation of the navigability in a scene. Talk presented at the 13th annual meeting of the Vision Sciences Society, Naples, FL.

Peigneux, P., Laureys, S., Fuch, S., Collette, F., Perrin, F., Reggers, J., Phillips, C., Degueldre, C., Del Fiore, G., Aerts, J., Luxen, A., & Maquet, P. (2004). Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron, 44*(3), 535–545.

Pober, B. R., & Filiano, J. J. (1995). Association of chiari malformation and Williams syndrome. *Pediatric Neurology, 12*, 84–88.

Prados J., & Trobalon, J. B. (1998). Locating an invisible goal in a water maze requires at least two landmarks. *Psychobiology, 26*, 42–48.

Ranck, J. B. (1986). Head direction cells in the deep cell layer of dorsal presubiculum in freely moving rats. In G. Buzsáki & C. H. Vanderwolf (Eds.), *Electrical activity of the archicortex* (pp. 217–220). Budapest: Akademai Kiado.

Rauchs, G., Orban, P., Balteau, E., Schmidt, C., Degueldre, C., Luxen, A., Maquet, P., & Peigneux, P. (2008). Partially segregated neural networks for spatial and contextual memory in virtual navigation. *Hippocampus, 18,* 503–518.

Reiser, J. J., Pick, H. L., Ashmead, D. H., & Garing, A. E. (1995). Calibration of human locomotion and models of perceptual-motor organization. *Journal of Experimental Psychology: Human Perception and Performance, 21*, 480–497.

Reiss, A. L., Eliez, S., Schmitt, J. E., Straus, E., Lai, Z., Jones, W., & Bellugi, U. (2000). Neuroanatomy of Williams syndrome: a high-resolution MRI study. *Journal of Cognitive Neuroscience, 12*, 65–73.

Rodrigo T., Chamizo, V. D., McLaren, I. P. L., & MacKintosh, N. J. (1997). Blocking in the spatial domain. *Journal of Experimental Psychology: Animal Behavior Processes, 23*, 110–118.

Rolls, E. T., Stringer, S. M., & Elliot, T. (2006). Entorhinal cortex grid cells can map to hippocampal place cells by competitive learning. *Network, 17*, 447–465.

Rosenbaum, R. S., Winocur, G., Grady, C. L., Ziegler, M., & Moscovitch, M. (2007). Memory for familiar environments learned in the remote past: fMRI studies of healthy people and an amnesic person with extensive bilateral hippocampal lesions. *Hippocampus, 17*, 1241–1251.

Rosenbaum, R. S., Ziegler, M., Winocur, G., Grady, C. L., & Moscovitch, M. (2004). "I have often walked down this street before'': fMRI studies on the hippocampus and other structures during mental navigation of an old environment. *Hippocampus, 14*, 826–835.

Rosenberg, D. R., Sweeny, J. A., Gillen, J. S., Kim, J., Varanelli, M. J., O'Hearn, K. M., Erb, P. A., Davis, D., & Thulborn, K. R. (1997). Magnetic resonance imaging of children

without sedation: preparation with simulation. *Journal of the American Academy of Child Adolescent Pscyhiarty, 36*(6), 853–859.

Ross, R. S., & Slotnick, S. D. (2008). The hippocampus is preferentially associated with memory for spatial context. *Journal of Cognitive Neuroscience, 20*, 432–446.

Rushworth, M. F., Behrens, T. E., & Johansen-Berg, H. (2006). Connection patterns distinguish 3 regions of human parietal cortex. *Cerebral Cortex, 16*, 1418–1430.

Sargolini, F., Fyhn, M., Hafting, T., McNaughton, B., Witter, M. P., Moser, M-B., & Moser, E. I. (2006). Conjunctive representation of position, direction, and velocity in entorhinal cortex. *Science, 5,* 758–762.

Sarpal, D., Buchsbaum, B. R., Kohn, P. D., Kippenhan, J. S., Mervis, C. B., Morris, C. A., Meyer-Lindenberg, A., & Berman, K. F. (2008). A genetic model for understanding higher order visual processing: functional interactions of the ventral visual stream in Williams syndrome. *Cerebral Cortex, 18*(10), 2402–2409.

Savelli, F., & Knierim, J. J. (2010). Hebbian analysis of the transformation of medial entorhinal grid cell inputs to hippocampal place fields. *Journal of Neurophysiology,* 103, 3167–3183.

Savelli, F., Yoganarasimha, D., & Knierim, J. J. (2008). Influence of boundary removal on the spatial representations of the medial entorhinal cortex. *Hippocampus, 18,* 1270–1282.

Schinazi, V. R., & Epstein, R. A. (2010). Neural correlates of real-world route learning. *Neuroimage, 53*, 725–735.

Schinazi, V. R., Nardi, D., Newcombe, N. S., Shipley, T., & Epstein, R. A. (2013). Hippocampal size predicts rapid learning of a cognitive map in humans. *Hippocampus, 23,* 515–528.

Sereno, A. B., & Lehky, S. R. (2011). Population coding of visual space: comparison of spatial representations in dorsal and ventral pathways. *Frontiers in Computational Neuroscience, 4*, 1–16.

Segura-Puimedon, M., Sahún, I., Velot, E., Dubus, P., Borralleras, C., Rodrigues, A. J., Valero, M. C., Valverde, O., Sousa, N., Herault, Y., Dierssen, M., Pérez-Jurado, L. A., & Campuzano, V. (2014). Heterozygous deletion of the Williams-Beuren syndrome critical interval in mice recapitulates most features of the human disorder. *Human Molecular Genetics*, *23*(24), 6481–6494.

Sharp, P. E. (2006). Subicular place cells generate the same "map" for different environments: comparison with hippocampal cells. *Behavioural Brain Research, 174*, 206–214.

Shettleworth, S. J. (2010). *Cognition, evolution, and behavior*. New York: Oxford University Press.

Shusterman A., Lee, S. A., & Spelke, E. (2008). Young children's spontaneous use of geometry in maps. *Developmental Science, 11*(2), F1–F7.

Si, B., & Treves, A. (2009). The role of competitive learning in the generation of DG fields from EC inputs. *Cognitive Neurodynamics*, *3*, 177–187.

Solstad, T., Boccara, C. N., Kropff, E., Moser, M-B., & Moser, E. I. (2008). Representation of geometric borders in the entorhinal cortex. *Science, 322*, 1865–1868.

Solstad, T., Edvard I., Moser, M., & Einevoll, G. T. (2006). From grid cells to place cells: a mathematical model. *Hippocampus, 16*, 1026–1031.

Sovrano, V. A., Bisazza, A., & Vallortigara, G. (2003). Modularity as a fish (Xenotoca eiseni) views it: conjoining geometric and nongeometric information for spatial reorientation. *Journal of Experimental Psychology in Animal Behavioral Processes*, *2*9, 199–210.

Spelke, E. S. (2000). Core knowledge. *American Psychologist, 55*(11), 1233-1243.

Spiers, H. J., Burgess, N., Hartley, T., Vargha-Khadem, F., & O'Keefe, J. (2001). Bilateral hippocampal pathology impairs topographical and episodic memory but not visual pattern matching. *Hippocampus, 11*, 715–725.

Spiers, H. J., & Maguire, E. A. (2006). Thoughts, behaviour, and brain dynamics during navigation in the real world. *Neuroimage, 31*, 1826–1840.

Squire, L. R., Stark, C. E., & Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience, 27*, 279–306.

Stackman, R. W., & Taube, J. S. (1997). Firing properties of head direction cells in the rat anterior thalamic nucleus: dependence on vestibular input. *Journal of Neuroscience, 17,* 4349–4358.

Stewart, S., Jeewajee, A., Wills, T. J., Burgess, N., & Lever, C. (2013). Boundary coding in the rat subiculum. *Philosophical Transactions of the Royal Society, Biological Sciences, 369*(1635), 20120514.

Strømme, P., Bjornstad, P. G., & Ramstad, K. (2002). Prevalence estimation of Williams syndrome. *Journal of Child Neurology*, *17*, 269–271.

Summerfield, J. J., Hassabis, D., & Maguire, E. A. (2010). Differential engagement of brain regions within a "core" network during scene construction. *Neuropsychologia, 48*, 1501–1509.

Sutton, J. E. (2006). The development of landmark and beacon use in young children: evidence from a touchscreen search task. *Developmental Science 9*(1), 108–123.

Sutton, J. E., Joanisse, M. F., & Newcombe, N. S. (2010). Spinning in the scanner: neural correlates of virtual reorientation. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 36*(5), 1097–1107.

Suzuki, W. A., & Amaral, D. G. (1994). Perirhinal and parahippocampal cortices of the Macaque monkey: cortical afferents. *Journal of Comparative Neurology, 350*, 497–533.

Suzuki, K., Yamadori, A., Hayakawa, Y., & Fuji, T. (1998). Pure topographical disorientation related to dysfunction of the viewpoint dependent visual system. *Cortex, 34*, 589–599.

Tae, W.S., Joo, E. Y., Kim, J. H., Han, S. J., Suh, Y.-L., Kim, B. T., Hong, S. C., & Hong, S. B. (2005). Cerebral perfusion changes in mesial temporal lobe epilepsy: SPM analysis of ictal and interictal SPECT. *Neuroimage, 24*, 101–110.

Takahashi, N., & Kawamura, M. (2002). Pure topographical disorientation: the anatomical basis of landmark agnosia. *Cortex, 38*, 717–725.

Taube, J. S. (1998). Head direction cells and the neurophysiological basis for a sense of direction. *Progress in Neurobiology, 55*, 225–256.

Taube, J. S. (2007). The head direction signal: Origins and sensory-motor integration. *Annual Reviews of Neuroscience, 30,* 181–207.

Taube, J. S., Muller, R. U., & Ranck, J. B. (1990). Head-direction cells recorded from the postsubiculum in freely moving rats. *Journal of Neuroscience, 10,* 420–435.

Taylor, K. J., Henson, R. N., & Graham, K. S. (2007). Recognition memory for faces and scenes in amnesia: dissociable roles of medial temporal lobe structures. *Neuropsychologia, 45,* 2428–2438.

Thomas, C., Avidan, G., Humphreys, K., Jung, K., Gao, F., & Berman, M. (2009). Reduced structural connectivity in ventral visual cortex in congenital prosopagnosia. *Nature Neuroscience, 12*, 29–31.

Thomas, K. M., & Casey, B. J. (1999). Functional MRI in pediatrics. In C. Moonen and P. A. Bandettini (Eds.), *Medical Radiology, Functional MRI* (pp. 513–523). New York, NY: Springer-Verlag.

Todd, J. J., & Marois, R. (2004). Capacity limit of visual short-term memory in human posterior parietal cortex. *Nature, 428*, 751–754.

Tolman, E. C. (1948). Cognitive maps in rats and men. *Psychological Review, 55*, 189–209.

Tomaiuolo, F., Di Paola, M., Caravale, B., Vicari, S., Petrides, M., & Caltagirone, C. (2002). Morphology and morphometry of the corpus callosum in Williams syndrome: a T1-weighted MRI study. *Neuroreport, 13*, 2281–2284.

Tommasi, L., Chiandetti, C., Pecchia, T., Sovrano, V. A., & Vallortigara, G. (2012). From natural geometry to spatial cognition. *Neuroscience & Biobehavioral Reviews, 36*, 799–824.

Troiani, V., Stigliani, A., Smith, M. E., & Epstein, R. (2012). Multiple object properties drive scene-selective regions. *Cerebral Cortex, 24*(4), 883–897.

Uddin, L. Q., Supekar, K., Amin, H., Rykhlevskaia, E., Nguyen, D. A., Greicius, M. D., & Menon, V. (2010). Dissociable connectivity within human angular gyrus and intraparietal sulcus: evidence from functional and structural connectivity. *Cerebral Cortex, 20*, 2636–2646.

Ungerleider, L. G., & Mishkin, M. (1982). Two cortical visual systems. In D. J. Ingle, M. A. Goodale & R. J. W. Mansfield (Eds.), *Analysis of visual behavior* (pp. 549–86). Cambridge, MA: The MIT Press.

Utsunomiya, H., Takano, K., Okazaki, M., & Mitsudome, A. (1999). Development of the temporal lobe in infants and children: analysis by MR-based volumetry. *American Journal of Neuroradiology, 20,* 717–723.

Uttal, D. H., Gregg, V. H., Tan, L. S., Chamberlin, M. H., & Sines, A. (2001). Connecting the dots: Children's use of a systematic figure to facilitate mapping and search. *Developmental Psychology, 37*, 338–350.

Vallortigara, G., Zanforlin, M., & Pasti, G. (1990). Geometric modules in animal's spatial representation: a test with chicks. *Journal of Comparitive Psychology*, *104*, 248–254.

Van Essen, D. C. (2004). Towards a quantitative, probabilistic neuroanatomy of cerebral cortex. *Cortex, 40,* 211–212.

Vargas, J. P., Lopez, J. C., Salas, C., & Thinus-Blanc, C. (2004). Encoding of geometric and featural spatial information by goldfish (Carassius auratus). *Journal of Comparitive Psychology, 118*, 206–216.

Vasilyeva, M., & Bowers, E. (2006). Children's use of geometric information in mapping tasks. *Journal of Experimental Child Psychology, 95*(4), 255–277.

Wang, R. F., & Spelke, E. S. (2002). Human spatial representation: insights from animals.

Trends in Cognitive Sciences, 6, 376–382.

Whishaw, I. Q., & Mittleman, G. (1986). Visits to starts, routes, and places by rats (Rattus norvegicus) in swimming pool navigation tasks. *Journal of Comparative Psychology, 100*, 422–431.

Wills, T. J., Cacucci, F., Burgess, N., & O'Keefe, J. (2010). Development of the hippocampal cognitive map in pre-weanling rats. *Science, 328*, 1573–1576.

Wolbers, T., & Hegarty, M. (2010). What determines our navigational abilities? *Trends in Cognitive Sciences, 14,* 138–146.

Yi, D.-J., Turk-Browne, N. B., Flombaum, J. I., Kim, M.-S., Scholl, B. J., & Chun, M. M. (2008). Spatiotemporal object continuity in human ventral visual cortex. *Proceedings of the National Academy of Sciences (USA)*, 105.

Zachariou, V., Klatzky, R., & Behrman, M. (2013). Ventral and dorsal visual stream contributions to the perception of object shape and object location. *Journal of Cognitive Neuroscience, 26*(1), 189–209.

Zukowski A. (2009). Elicited production of relative clauses in children with Williams syndrome. *Language and Cognitive Processes, 24*, 1–43.

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